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Studies on Schistosomiasis Japonica

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With a Supplement on the Molluscan Hosts of the Human Blood Fluke in China and Japan, and Species Liable to be Confused With Them

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To

HENRY SPENCER HOUGHTON

Director of the Peking Union Medical College, who, as a former medical missionary at Wuhu, Anhwei Province, China, undertook the first scientific study of schistosomiasis japonica in China, this study is affectionately dedicated

FOREWORD.

The investigations embodied in the main sections of this monograph on schistosomiasis japonica have been a cooperative undertaking, in which certain of the problems have involved a major responsibility in medical zoology, while others have been primarily clinical in their nature. Doctor Meleney deserves particular credit for the sections on the course of migration of *Schistosoma japonicum* within the mammalian host (III), the pathological anatomy of schistosomiasis japonica (VI), and clinical schistosomiasis (VII), as well as for the first discovery of the molluscan host in China and portions of the section on prophylaxis, and had the sections been published as separate papers, such credit for his work would have been appropriately indicated. It remains for me to say that without Doctor Meleney's whole-hearted and painstaking cooperation many significant phases of the problem would have been left unstudied and certain facts would have been overlooked.

Doctor Annandale's valuable revision of the molluscan species involved as intermediate hosts of *Schistosoma japonicum* (Appendix A) arrived after the monograph was in press. Since this treatise on the molluscan group in question proves conclusively that the genus Blanfordia is not known to be involved in schistosomiasis japonica, it has seemed wise to substitute in the body of the monograph the term Katayama, which Robson first used (1915) in describing the species from Japan, for the term Blanfordia. The more technical recognition of Katayama as a subgenus or section of the genus Oncomelania is a point requiring common usage among specialists working on mollusca before its introduction into medical literature should be advocated.

I wish to express our appreciation to Doctor William H. Welch, the editor of the American Journal of Hygiene, for undertaking the publication of this monograph, and to the managing editor, Doctor Charles E. Simon, for his constant and sympathetic interest in the project.

E. C. F.

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Family Rissoidae. Subfamily Triculinae nov. Genus *Tricula*. *Taihua*, genus nov. Genus *Oncomelania*. Section Katayamae (*Oncomelania nosophora*, *O. formosana*). Section Hemibiae (*Oncomelania hupensis*, *O. sublevis*, *O. longiscata*). Subfamily Pomatiopsinae. Genus *Blanfordia*.

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STUDIES ON SCHISTOSOMIASIS JAPONICA.*

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Perusal of the known facts on the subject of schistosomiasis japonica indicates that several gaps in our knowledge of the disease and of the causative organism still exist. These gaps occur (1) with respect to the morphology and biology of the developmental stages of the three generations of the worm; (2) in the physiological relation of the worm to and its pathological effect on the intermediate and definitive hosts; (3) in the present distribution of the disease in the Orient and the environmental conditions (both climatic and edaphic) governing such distribution; and (4) in respect to therapy and control of the disease. We have undertaken this study in an attempt to solve certain of these unfinished phases of the problem, particularly with reference to the disease, as it exists in China. Our findings will be presented under the following headings:

I. Historical aspects of the problem.
II. Morphology, biology and life history of the causative organism, *Schistosoma japonicum* Katsurada.
III. The route of migration of *Schistosoma japonicum* in the body of the mammalian host.
IV. The intermediate hosts of *Schistosoma japonicum* and their known relation to schistosomiasis japonica in the Orient.
V. The distribution of schistosomiasis japonica in the Orient.
VI. The pathological anatomy of schistosomiasis japonica.
VII. Clinical schistosomiasis in man and animals.
VIII. Prophylactic aspects of schistosomiasis japonica.

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I. HISTORICAL ASPECTS OF THE PROBLEM.

Schistosomiasis japonica is a disease probably as old as Egyptian bilharziasis. But while there is accurate evidence of the existence of the latter during the reign of the Pharaohs and there are definite data on its etiology for more than half a century, exact knowledge regarding Japanese schistosomiasis dates back less than four decades. Following the discovery and naming of the causative organism, *Schistosoma japonicum*, by Katsurada in 1904, and the publication of the clinical and pathological pictures of the disease in Japan, workers in other countries in the Far East soon found the worm and recognized it as the essential agent in the production of the disease in their respective countries. Thus Catto (1905) reported the disease in a Chinese at Singapore, although the case is known to have come from Fukien, a coastal province of China adjacent to Formosa. It was likewise recognized soon after this in China (Logan, 1905) and in the Philippines (Wooley, 1906). The course of events in the discovery of the parasite in these several centers in the Far East, together with the various aspects of its life history, morphological, biological, pathological, clinical and sanitary, is as interesting as it is important in the annals of medical literature. Inasmuch as some of this work is still closed to the Western scientific world, because it is published in Japanese, or because it has never been published at all, it seems wise to summarize the course of development by which certain phases of the problem of schistosomiasis japonica have been solved and to correlate these with the data which we are presenting in our study.

The earliest recorded account of schistosomiasis japonica is that of Fujii (1847) who described the disease in the Katayama district. Later Baelz (1883), a sometime professor in the Imperial University at Tokyo, who described the endemic area of Okayama, pictured the conditions under which the people lived in this region, and presented his information on certain villages which he had surveyed in the endemic area. He found the infective incidence to be about 20 per cent. He listed the clinical symptoms (enlargement of the liver and spleen, bloody diarrhea, anemia, fever, cachexia, ascites and edema), which with our present knowledge definitely delimit the disease, described as schistosomiasis japonica. However, he attributed the infection to the lesser liver fluke, *Clonorchis sinensis* (*Distoma hepatis endemicum s. perniciosum*). Likewise, the pathological picture obtained from a

study of autopsy material containing infection with *Clonorchis sinensis*, was misinterpreted as being related to the Okayama infection.

The first actual relation of the causative agent, the oriental blood-fluke, to the infection was secured by Katsurada (1904), although Yamagiwa (1890), Kurimoto (1893), Fujinami (1904) and others had previously found eggs of an unknown parasite in various organs (particularly the liver) of individuals who had died in infected areas and believed them to play the etiological rôle in the disease. Kasai (1903) first found the eggs in the feces. Fujinami (1907) obtained a single female worm in the portal vein of the liver of man in May 1904, which he believed to be the first specimen found.

Katsurada first studied material in April 1904 in Yamanashi Province. In the stools of five out of 12 patients studied he found eggs of a uniform character, similar to those now described as of *Schistosoma japonicum*. He anticipated from the clinical symptoms "that the disease was caused by these eggs and the mother worms and that the latter were apparently present in the portal system." Since he was able to obtain no autopsies and had already confirmed the presence of the human parasites, *Clonorchis sinensis* (*D. spathulatum*) and *Paragonimus westermani* (*D. westermanni*), in dogs and cats, he thought he might find this parasite also in these animals. He dissected two dogs and one cat, and from the latter secured a piece of a male worm (observations published in Japanese on June 30, 1904). Later he secured many specimens in the portal system of a second cat (published in Japanese on August 13, 1904), and at this time named the species *Schistosomum japonicum* (German account, December, 1904).

Katsurada then gave an accurate description of the eggs, as found in the feces of man and cat, as well as from the uterus of the mother worm. He also described the male and female parent worms and the pathological picture of the disease.

In the same year (1904) Tsuchiya found the parasites in dogs, cats and men. In 1904 Kasai and Ogawa described the clinical phases of the disease. In 1905 Fujinami and Nozaki (Fujinami, 1907) investigated the disease in the cow, while Fujinami had worked out by 1907 the pathological anatomy of the infected tissues, and the habitat of the adult worm, namely, in the mesenteric veins, in the portal vein including its branches in the liver, and in the splenic vein.

"The adult females wander into the delicate intestinal venules and lay their eggs, which either remain *in situ* in the blood vessels or are apparently capable of penetrating through the thin venule wall

into the tissues. . . . Some of the eggs are transported centrally and thus arrive in the liver." Through this channel, he argues, the eggs are carried to the lungs and brain and arterial system.

Thus the morphology of the adult worms in the portal system, together with the pathological and clinical pictures, were speedily worked out and became known facts within three years after the worm was first described by Katsurada. But the course of development of the worm, both previous to invasion of the mammalian host and from the time of invasion to the time of maturity in the portal vessel, were still to be determined. The route of invasion was also still unknown. Infection was considered at this time by most Japanese investigators to occur, probably, by way of the mouth. In order to test the mouth and skin as possible portals of entry, Fujinami and Namakura (1909), working in the Katayama endemic area in Hiroshima Province, exposed certain experimental animals (calves, dogs and cats) to rice field water which was thought to be the carrier of the infection. Certain of these animals were placed knee-deep in the "infected water"; others in the same situation had their legs disinfected and covered; still others were allowed to wade in the $5\frac{1}{2}$ inch canals, watering the rice fields. Another group was provided with leg protectors and allowed to crop the grass and drink the water from infected areas. One group was allowed to drink and eat at random in the rice fields, and a final group was kept as a control. The experiments showed conclusively that the route of infection was by way of the skin. Incidentally these investigators were able to produce all stages of infection of the young worm in the portal vein by allowing continuous infection to take place. Cattle, horses, dogs and cats as well as man were found to be natural hosts of the worm. The writers were likewise able to advance the first rule of prophylaxis in infected areas, namely, adequate protection of the skin of exposed animals.

By 1911 Fujinami and his associates found that guinea-pigs, monkeys and white rats were also susceptible to experimental infection with *Schistosoma japonicum*.

Meanwhile Miyagawa (1912) had been working on the route of infection between the time the worm entered the body through the skin and its arrival in the portal veins. He believed that neither the lymph channels nor the connective tissue were the path of migration, but rather the venous system. To test his hypothesis he attempted to recover schistosomula from the peripheral veins. The results of his work were published in 1912. He examined blood taken from the femoral and saphenous veins of infected animals in two ways.

(1) Thick blood smears were allowed to dry and were then washed with distilled water to wash out the red cells. The residue was then examined for worms. (2) Other blood samples were washed in normal saline and the precipitate examined. He was able to recover from the superficial veins small worms, about 40 μ long by 15 to 22 μ wide, and successively larger. He noted that the forks of the gut united distad in worms about 300 μ long. Although he regarded his worm as a digenetic trematode at this period, his description of the probable life history is clearly that of a monogenetic form. He compared the young worm, part for part, with the miracidium, confusing the spines of the young fluke with the cilia of the miracidium. But Miyagawa finally concluded (l. c., p. 415) that "the invasion form of *Schistosoma japonicum* is much smaller than the miracidium. It has shorter cilia." . . . For these reasons he concluded "that the invasion form is not identical with the miracidium arising from the egg, but with that into which, through a change of generation, the miracidium develops in another (and) intermediate host."

A year later Miyagawa (1913) was obliged to modify his theory of the path of migration of the schistosome larva through the body, to include the lymph channels, since he was able to obtain young worms by tying off lymph channels. He likewise obtained young worms from sections of inguinal glands.

While Miyagawa was continuing his interesting experimental work on the invasion route of the schistosome, Miyairi and Suzuki (Miyairi, 1913, 1914, 1914*a*, Miyairi and Suzuki, 1913, 1914) were making progress along a similar line in a separate endemic area in Kyushu Province. They were able not only to infect mammals from cercariae obtained from Katayama snails which they had found to be the intermediate host in Kyushu Province, but were also, in turn, able to observe the penetration of the hatched miracidia into the same species of snail and to find from time to time the development within the snail by dissecting infected snails. This information was later published in more complete form (1914). Miyairi and Suzuki described the snail host in detail, classifying it as far as the family Hydrobiidae. The miracidia were hatched from eggs obtained from an infected calf's dung and were observed to infect within two hours all snails submitted to infection. They traced the transformation of the miracidium into the first generation sporocyst and observed spines on the anterior end of the second generation sporocyst ("redia" of these investigators). The third generation larvae (cercariae) were then allowed to infect mice to complete the experimental history. Contemporaneously, but indepen-

dently Miyagawa had verified the belief that *Schistosoma japonicum* had a molluscan intermediate host, basing his theory on Odhner's work on Sanguinicola (1911), a distantly related form. He was able to prove Katayama to be the mollusc by a series of exclusion experiments. The cercaria found to infect experimental animals was shown to be a fork-tailed larva and to have relations much closer to the young worms in the definitive host than to the miracidium.

Later workers in Japan have devoted considerable time to the more detailed study of the path of invasion which the worm takes through the body of the definitive host and to sanitary measures connected with prophylaxis. *Schistosoma japonicum* was found to penetrate the skin and either enter the lymph spaces or the small venules of the skin, in either event reaching the right heart and shortly thereafter the lung capillaries. Two schools of opinion have arisen as to the course of the worms from the pulmonary arteries to the portal system. Narabayashi (1916) believed that the worms leave the lungs, pass from the pleural cavity through the mediastinum and diaphragm and thence reach the liver and portal system. Sueyasu (1920), working with serial sections of infected mice, found that many of the schistosomules which reach the lungs break through the lung tissue, crawl into the pleural cavity and reach the diaphragm, from which region, as he argued, they (1) either enter the liver direct, or (2) having penetrated through the diaphragm into the abdominal cavity, reach the liver and at length come to lie in their final place of residence, the portal system. On the other hand, Miyagawa and Takemoto (1918, 1921) believed the worms were delayed for a short time in the capillaries of the lungs, after which they entered the left heart and were carried into the arterial system, a portion of them at least being "carried through the aorta to the wall of the gastrointestinal canal, after passing through which they reach their permanent residence (the portal branches in the liver) by the mesenteric veins." On the other hand, a few were believed to enter directly into the hepatic artery, and in this way reach the liver.

Work of prophylaxis in endemic centers in Japan has consisted almost exclusively of experimenting on the value of chemicals in destroying the snail host, although Miyagawa (1916) has tested the resistance of the schistosome eggs to various chemicals. Of all the chemicals tried, lime has been found the surest and most economical (Miyagawa, 1913*a*, Narabayashi, 1916, and Fujinami and Sueyasu, 1919).

Fujinami and Sueyasu (l.c.) proposed an extensive program to eradicate the disease, particularly with respect to exterminating the larva and the larval host (the snail). For this purpose they tried cal-

cium oxide, calcium chloride and calcium hypochlorite. Of these three calcium oxide was found to be the most effective.

Quinine hydrochloride was found to be potent in treating the disease, but arsenicals and mercury preparations gave negative results in experimental therapy (Miyagawa, 1912).

During a visit to China and Japan for the purpose of connecting the problem of schistosomiasis japonica with that of the Egyptian bilharziasis Leiper and Atkinson (1915) repeated the experimental work of Miyairi and Suzuki and of Miyagawa and were able, from Japanese material, to verify the work of the Japanese investigators. They failed, however, to discover the molluscan intermediate host in the endemic area which they visited in China (i.e., Soochow-Kashing).

As has frequently been the case in many important contributions to science, several workers attack the same problem contemporaneously, but without knowledge of each other's investigations. Only the circumstance of time gives one the honor which the other quite equally deserves. Such is the case with *Schistosoma japonicum* Katsurada, for had the publication of Katsurada's discovery (Dec., 1904) been delayed, the credit would have been given, no doubt, to Catto, who announced his discovery of the worm in January, 1905. Catto's material was obtained from an autopsy on a Chinese man from Fukien Province who died of cholera at Singapore. Whether or not the Chinese was a native of Fukien and had obtained his infection there remains in doubt. This investigator first confused the ova of the worms in the tissues with coccidia, but later corrected his error, although he was undoubtedly mistaken in thinking he found the adult worms in the mesenteric arteries as well as the mesenteric veins.

Information on schistosomiasis japonica from China during the decade following the naming of the causative organism by Katsurada in 1904 was confined almost entirely to the discovery of the disease in various centers in the Yangtze Valley and its tributaries. Logan (1905), learning of Katsurada's and Catto's work, was able to find the typical eggs of *S. japonicum* in the stools of a patient suffering from bloody diarrhea, cachexia, enlargement of the liver and distention of the superficial veins of the abdomen. This finding was verified by Katsurada in a private communication. Logan found the disease on the west side of Tung Ting Lake, a lateral branch of the Central Yangtze, far up its course. Following Logan, Taylor (1907), Peake (1909) and Houghton (1909) reported cases from Anhwei and Hunan Provinces, while the Research Committee of the China Medical Missionary Association, in its Third and Fourth Interim Reports (1910, 1910*a*),

showed the disease to exist in various centers of Hunan, Hupeh, Anhwei, Kiangsu, and Chekiang Provinces and in Hongkong, and other reports for 1911 showed it to be present in Kiangsi Province. In 1910, Houghton published an account of his studies on the clinical pathology of the disease, as it occurred in Anhwei Province, and described the Anhwei area of the infection. More recently Vickers (1920) stated that schistosomiasis had been established on the North Branch of the West River, above Canton.

Whereas the infection was commonly known in Japan as "Okayama" or "Katayama" disease, depending on the area in which it occurred, in China it was known as "Yangtze Valley Fever," "Hankow Fever," "Kiukiang Fever" and "Urticarial Fever" (Logan, 1912).

Although a considerable amount of information exists in China as common knowledge by the foreign practitioners, little has been published. It is, therefore, our purpose in later papers of this series to assemble as much of this information as seems advisable, and though the geographical distribution and clinical features of the disease, as it exists in China, may even then be incomplete, it is believed that the compilation of this information will mark a forward step.

Information on the work of Katsurada reached the Philippines shortly after its publication, and Woolley (1906) confirmed the presence of the infection in natives of the Islands, particularly the island of Leyte. In a later study Garrison (1908) recorded the infection on Samar, Leyte and Mindanao Islands.

While the adult worm, *Schistosoma japonicum*, was adequateiy studied by the early Japanese investigators, the first accurate and complete account of the cercaria, its morphology and biology, was published by Cort (1919) from Japanese snails which had been shipped in dry earth, and were thus shown to withstand a considerable amount of desiccation. Cort's study (1921) of the young worms in the tissues of experimental mice has added materially to the available information on the development of the worm in the adult host.

In conclusion of this section, we take the opportunity of expressing our thanks to Professors A. Fujinami, F. Katsurada, K. Miyairi, Y. Miyagawa and H. Kobayashi, for their generosity in providing us with original papers dealing with the problem of schistosomiasis japonica in Japan.

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II. MORPHOLOGY, BIOLOGY AND LIFE HISTORY OF THE CAUSATIVE ORGANISM, *SCHISTOSOMA JAPONICUM* KATSURADA.

(Plates I to XII.)

While the essential data relating to the Oriental blood-fluke, *Schistosoma japonicum*, are now known, we have found in studying the problem many points in the structure and biology of the several phases of the life cycle of the worm which need further consideration. Moreover, a clear knowledge of certain structures of the worm has explained to us obscure or unknown phases of the clinical and preventive parts of the problem. We feel justified, therefore, in presenting our information in considerable detail, knowing its intimate bearing on the more practical aspects of the study.

For convenience, as well as to preserve the logical chronology of the life cycle, we shall take up the data under the following heads:

A. The egg-miracidium phase of the life cycle.
B. The developmental cycle within the mollusc host.
C. The cercaria.
D. The adult schistosome in the definitive host.

A. The egg-miracidium phase of the life cycle.

(Figs. 1–10, Photomicrographs 1–14.)

The fertilized egg of *Schistosoma japonicum*, in the uterus of the adult female worm, and the same egg in the feces of the definitive host, are structurally quite different objects. The former is an ovoid, hyaline, double-convex disc or lens, measuring on the average 67 μ in length by 50 μ in width, with a slight depression on one side near the anterior end, from which depression an abbreviated curved hook or spine typically arises (Fig. 1; Photomicrographs 1, 2). This hook is more readily recognized in the egg shell at this stage than in the shell of the more mature larva. We have found it readily in all specimens, mature and immature, from Japanese material and have recognized it in mature eggs from all Chinese cases in which we have made careful search.

At the time of oviposition the egg is complete, but may not be fertilized. It contains a large oocyte with homogeneous cytoplasm and a

number of yolk cells, rich in large granules of a lecithin nature, which stain deeply with cresyl blue. In case fertilization is about to be accomplished, but has not been completed, several motile spermatozoa are usually found within the egg shell.

The egg is deposited by the female worm in the wall of the gut, at a point as far in toward the mucosa as the worm is able to migrate in order to carry out this function. The subject of the deposition of the egg and its discharge into the lumen of the gut will be dealt with in a later paper of this series, and will, therefore, not be further discussed at this time. Suffice it to say that the degree of development of the miracidium within the egg, before its appearance in the feces, depends largely upon the amount of time required for the egg to pass from the point of deposition to the lumen of the gut. In acute stages of the disease the eggs are found most abundantly in flecks of bloody mucus which are passed in the stool (Photomicrograph 3), and these eggs are likely to contain immature miracidia (Photomicrographs 4, 5, 6), while the ova discharged in more normal stools, in later stages of the disease, are more likely to contain miracidia which are all practically mature.

Immature eggs in the feces.

In animals infected with *Schistosoma japonicum* crops of eggs appear in the feces, along with flecks of bloody mucus, shortly after the worms mature in the mesenteric veins. In experimental dogs we have found these first eggs as early as twenty-nine days after exposure to infection. These first eggs are usually immature and in a heavy infection afford adequate material for study of the growth and development of egg and enclosed larva. At least eight distinct stages in development of this egg may be described, all but the first of which we have found in the first and second day's stools of dogs which were just beginning to show eggs in the feces. In addition to these, unfertilized eggs were common (Fig. 2).

The fertilized eggs, as deposited by the female worm, are about one-third longer than broad, and are quite regular except for the depression on one side, from which the abbreviated spine projects. The enclosed zygote behaves in the usual way by division into 2, 4, and 8 cells, without the discrete yolk cells entering directly into the embryo *sensu stricto*. The four-cell stage is the earliest found in the feces (Fig. 3). No growth in size has occurred, the yolk cells are still intact and the shell still presents the discoid contour. When the morula stage is reached, however (Fig. 4), the yolk cells have become partly digested, the spine becomes inflated at its base, causing it to be less

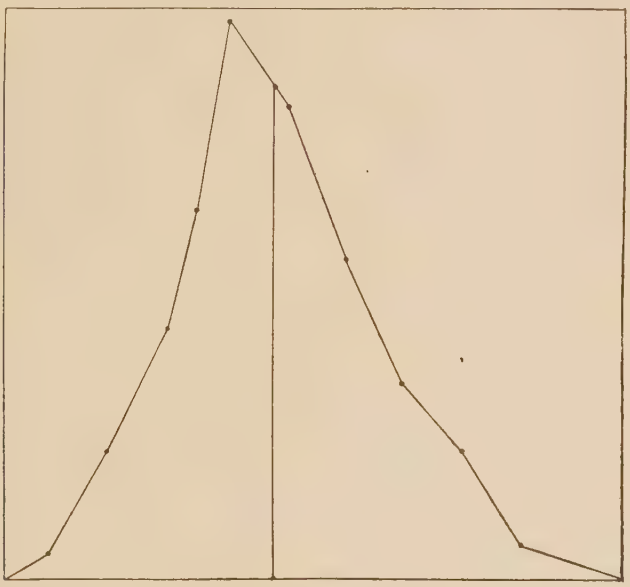
hooked, and the egg becomes rounded out. This latter process, by increasing the thickness of the egg, actually causes a temporary reduction in measurement of length and breadth. With the next step (Fig. 5) considerable growth of the embryo and stretching of the enveloping shell take place, although no differentiation of form results. Following this (Fig. 6) the embryo becomes elongated, while the first secretions from the embryo cause small particles of debris to stick to the gummy secretion around the shell. Next (Fig. 7, Photomicrograph 6) one sees an internal differentiation of organs, including the glands, and a considerable enlargement of the shell, so that a large amount of secretion may accumulate between the embryo and the shell. At the next stage (Fig. 8, Photomicrograph 7) all of the internal organs are present and are apparently functioning, and the larva is covered with the usual complement of cilia, although these are not yet beating. With the considerable freedom of movement which the larva enjoys within the shell, it may turn around, so that the spine appears posteriorly disposed (Photomicrograph 8, 9). With the acquisition of movement on the part of the cilia, the worm is mature. This function may not develop, however, until the egg is almost ready to hatch.

For several days after the first showers of eggs appear in the feces, undersized eggs with distinctly hooked spines and unorganized granular contents may be found in the feces. These are the unfertilized eggs (Fig. 2) which are commonly deposited in the first batch of eggs of the female worm, and which occurred not infrequently in all stools we have examined.

Size and shape of the mature egg in the feces.

Text books give a wide range of variation, both in length and width, of the mature egg. This is confirmed by our studies, but this variation is not based on a constant ratio of length to width, a ratio which is really of no fundamental importance. Our statement is based on our measurement of five hundred eggs taken from freshly passed stools of dogs, experimentally infected with cercariae obtained from infected snails from Kyushu Province, Japan, and checked by measurements of eggs from human cases, infected from four endemic centers in the Yangtze Valley. In this group all immature or non-viable specimens were discarded, while only those apparently normal were measured. Variation in lengths and widths, as well as the ratio between the two dimensions, was found to be considerable. Certain normal eggs were found to be almost spherical, while others were oval-elongate. But in uncompressed specimens the ratio of the several transverse diam-

eters (i.e. breadth) was consistently near 1:1. For this reason, in computing the curve of variation in size, it seemed advisable to use the products obtained by multiplying the length of each egg by the square of the width, giving, therefore, a series of computations comparable to the actual cubic contents of the eggs. The range of 525 such eggs is shown in Textfigure *A*. The curve is unimodal, indicating that the



TEXTFIGURE A. Curve of variability obtained from products of the measurements of the length, breadth and thickness of 500 mature eggs of *Schistosoma japonicum*.

series is a simple one, with no measurable differences in volume of the eggs, such as one might expect in a commingling of eggs of two or more series, races or species of helminths.

The mean for the 525 lengths, measured separately, in the series is 89.08 microns, while that of the breadths, measured similarly, is 66.66 microns. If one divides this length value (89.08) into the mean of the 525 *cubic values* (395,800) and takes the square root of the quotient the result is exactly the mean of the 525 breadths. This check proves that the arithmetical computations are correct. Furthermore, the method of the cubes, as described here, seems an accurate and reasonable one for estimating the mean value of helminth ova. Our results

show that the range of 525 normal eggs, measured for one series of worms of this species, is 74 to 106 microns in length by 60 to 80 microns in breadth or thickness, while the mean for these 525 eggs is 89.08 μ in length by 66.66 μ in breadth or thickness. The standard deviation for the unidimensional curves is $\pm$ 1.5, showing that although the range is large, only a very small share of the ova deviate any considerable distance from the mean, thus indicating that the series is particularly uniform.

These measurements are somewhat larger than those for fertilized ova *in utero* from this same series (ca. 67$\times$50 μ) and show that growth in volume has taken place in the interval. They are much higher than Manson-Bahr's figures (1921: 800, 801), which in themselves show considerable variation, since the size given in his text (p. 801) is 60 $\times$40 μ, and that in his comparative table (p. 800) is 70–75$\times$40–45 μ. Other manuals give size measurements equally varying one from the other.

Size of eggs of Schistosoma japonicum as quoted by several authors.

Braun-Seifert (1915) Vol. 1: 201 "Eggs oval, pale yellow, non-operculate, without terminal spine, according to age 0.075–0.09 mm. long, 0.053–0.075 mm. broad."

Castellani and Chalmers (1919): 592: "The eggs vary from 50 to 300, and *in utero* are soft, and so can form various shapes. *Ex utero* they are oval, faintly yellow, and double-contoured, 83.5$\times$62.5 microns, and have small lateral spines or thickenings and at the opposite side cap-like thickenings."

Fantham, Stephens, Theobald (1916): 279: "In feces the eggs measure 83.5 μ by 62.5 μ (man); 85 μ by 61.5 μ (cattle); 98.2 μ by 73.8 μ (dog). The eggs have either small lateral spines or thickenings, and Looss, at the opposite side, has described cap-like thickenings."

Manson-Bahr (1921): 800: "*S. japonicum.* Ova: Measurements: 70–75 μ long. 40–45 μ broad. Rounded. No spine-rudimentary lateral papilla." (801: The ova are oval in shape, 60 μ in length and 40 μ in breadth.)

Comparison of our series, from experimental material from dogs, with viable ova from human patients at Soochow, Nanking, Wuchang and Wuhu, which we have had an opportunity to measure, shows a difference to obtain here likewise. One Soochow series (fresh viable ova) had a mean average of 88 by 68 μ, practically identical with the experimental series, while one series, each from the four places named, had the respective measurements 80 by 58 μ, 80 by 60 μ, 76 by 58 μ, and 86

by 64 μ. We conclude, therefore, from all of these data that (1) the size variation of the ova of *S. japonicum* is very considerable, although there is a definite norm; (2) that the size is not determined by host, as certain workers have believed, but that (3) it depends on other factors not yet determined. The size of the parent worm may possibly be involved.

Moreover, another factor, that of capacity for stretching on the part of the egg shell or membrane, calls for consideration. The permeability of the shell, permitting fluid to enter it, is probably the only thing which could cause the shell to enlarge. This is no small matter. While it cannot be measured readily, it is perceptible at certain stages in the maturing of the miracidium. Not only the growth of the miracidium, but likewise the deposition of secretory and excretory products between the larva and the shell demand this distention. In the smaller egg, where little secretory material has been deposited, the shell is at times appreciably thicker and light yellowish-brown in color. In the eggs, where it has been enlarged to accommodate these several products, the shell is thin and practically colorless or with only a perceptible tinge of color.

All mature eggs from Japanese sources have the abbreviated hook or spine. It has been the opinion of many medical men in China that the egg of *Schistosoma japonicum* from Chinese sources lacks the spine. While it would be unsafe to generalize, we have found it in a more or less recognizable form on all eggs from Chinese material from several native endemic areas. In some cases it is similar to the typical hooked spine of the immature egg *in utero* from Japanese sources. In other cases it constitutes a short thumb-like projection. In still others the hook is almost obscured by a distinct enveloping structure.

The egg is frequently covered with a sticky material which collects debris from the surrounding mass, and in so doing obscures the shell and the contents of the egg. While direct proof yet remains to be found, it is not improbable that this secretion is from within the shell and may in part be a proteolytic ferment from the secretory glands within, that has been exuded through minute pores in the shell or dialized through the shell.

Development of the miracidium within the shell.

The miracidium is quite readily recognized in practically all schistosome eggs found in the stool. The head-end is developed into a truncated cone, while the four flame-cells, the germ cells and the cephalic glands are already developed. The production and differentiation of

the epidermal cilia is a later accomplishment. As the larva develops and differentiation progresses the miracidium comes more nearly to fill the shell. Furthermore there is a pouring out of mucoid proteolytic (?) secretion from the glandular elements of the larva which tends to form an inner mucous envelope for it. This secretion is particularly pronounced in the mucoid glands which empty through common groups of ducts ("anterior ducts" of authors) at the two sides of the worm (see Figs. 9, 11). It is probably this secretion which, permeating the shell membrane of the larva, exudes slowly from the shell and produces the characteristic stickiness noticed by observers both on fresh and preserved specimens.

Phenomena of hatching.

This phase of the subject has received little attention from investigators. There are several possible factors concerned in the hatching of the egg and the freeing of the miracidium. They may be divided into (1) internal and (2) external factors.

1. *Internal factors.*—First of all, in order that a viable miracidium may be hatched from the egg the miracidium must have reached maturity, so that, on hatching, it may live an independent free existence for a certain brief period. The rupture of the egg shell may be produced artificially in several ways without injuring the larva, which soon disintegrates, however, unless it is mature. Although this stage in development is a complex of several elements, it may be readily recognized by the ability of the cilia to take up movement immediately or shortly after rupture of the shell. Under unusual external conditions hatching may be retarded, so that ciliary movements may be seen in the unhatched miracidium. Such larvae are sometimes found in constipated stools. Considerable muscular activity likewise attends this stage of development (Photomicrograph 8). Not only is a restless back-and-forth movement of the larva seen in the mature unhatched egg, but the animal at times turns from end to end within the shell, frequently revolving many times (Photomicrographs 7, 8). This phenomenon in the miracidium of *Schistosoma japonicum* and of the other human schistosomes accounts for the fact that certain authors depict these larvae with spines located anteriorly, while others show them posteriorly. It seems quite evident that size, pressure, and movements of the mature miracidium play an important rôle in hatching, including both the rupture of the shell and the emergence of the miracidium. On the other hand, the secretions of the larva probably have no chemical effect on the shell, which is not dissolved even when deposited

in mammalian tissues, although these secretions no doubt tend to increase mass tension within.

It seemed necessary, likewise, to discover whether or not the lateral hook is related to the line of splitting of the shell, both in naturally and artificially hatched eggs. A study was made, therefore, of a large number of eggs of each type with the result that in each case of a single line splitting (the normal and usual process) the spine was found on the side opposite the cleavage line. Even in the few where the line of fracture was transverse or oblique the spine bore no relation to it. This is a reasonable procedure since the spine lies in an area of the shell which is thickened considerably more than the other regions and would, therefore, be most resistent. It shows, moreover, that the hook is not a factor in the hatching process.

2. *External factors.*—When once the miracidium is mature the external factors play an extremely important rôle in deciding whether or not normal hatching takes place. In fact it seems probable that in many instances of unfavorable environment viable miracidia rapidly degenerate. Among these conditions, tonicity, temperature, chemical constituents and fermentative agents of the medium are important determiners of the fate of the larva. Time and the stimulus obtained by agitation may also be factors involved.

(*a*) *Tonicity.*—All other factors being equal, isotonicity (i.e., the tonicity of mammalian serum) tends to prevent hatching, although no injury results to the larva. Hypotonicity of the medium causes hatching, with a rapid "popping" of the shell. If the larva is immature, death results; if it is mature, even distilled water does not cause degeneration or rupture. On the other hand, desiccation causes exosmotic phenomena, bringing about rapid collapse and death of the larva. This does not take place, however, without an attempt on the part of the larva to protect itself, for under such conditions there is an additional secretion of mucoid substances around the worm. This is a partial protection, although an imperfect one, for under laboratory conditions in Peking in April and May (relative humidity 5.0 to 40.0), eggs of *S. japonicum*, in feces in uncovered jars, died between the second and third days, while controls in covered jars survived for several days. On the fourth day the eggs in the desiccated stools had shrunken beyond all recognition. These eggs on the third day, when placed in distilled water, "popped" open, but non-viable larvae were extruded. Eggs remaining in constipated stools any length of time would likewise be subjected to a hypertonic medium.

While hypotonic solutions tend to produce hatching, hyper-

tonic solutions cause destruction of the larva. Miyagawa (1916: 466), using 5 per cent. sodium chloride, found plasmolysis of the miracidia to obtain very soon after immersing the eggs in the solution. Even then, he believed the egg to possess a certain selective protection against slight differences in osmotic pressure. We have observed shrinkage of the shell in strong sodium chloride and calcium chloride solutions, but have made no detailed study of this phase of the subject.

(*b*) *Temperature.*—Theoretically 37° C. is the optimum for the miracidia, since the eggs have developed at that temperature within the body of the host and since miracidia remaining within the body for any length of time have been observed by one of us (E. C. F.) to hatch. Under proper conditions we found miracidia to hatch readily at this point, although to our surprise they hatched equally well at room temperature (22° C.).

Miyagawa (1916: 460) found temperatures between 25° and 30° C. to be optimum for development. This corresponds with the range of summer temperature in Japan. He states that cool temperatures allow of little, if any, growth of the immature larva, while freezing kills the miracidium.

We ran a series of experiments to determine the upper and lower limits of temperature within which hatching of the miracidia took place. Eggs with motile miracidia from an acute case of schistosomiasis dysentery were used for the test. When washed carefully and left at room temperature (24° C.) most of these eggs hatched in from two to six hours. Controls were run for all experiments. In all cases washing was done with tapwater (from artesian wells).

Experiments to determine temperature limits for hatching of ova.
Series A.

Exp. 1. Eggs washed free of feces were immediately placed in the ice-chest at 8.5° C. for 20 hours. Upon removal they were examined and found to have a high percentage (about 50 per cent.) of active, free-swimming miracidia. A similar batch of eggs which was kept in the ice-chest at temperatures from 8° to 13° C. hatched almost completely over a period of twenty-eight days.

Exp. 2. Eggs were washed as in Exp. 1. and placed in the ice-chest at 4° C. for 20 hours. Upon removal the eggs were examined and found to be normal, but unhatched. The eggs were then placed at room temperature (23° C.) and observed from time to time. Normal hatching began six hours later and continued for four days.

Exp. 3. Eggs were washed as in Exp. 1. and placed in a test tube in

a freezing brine-ether mixture for one hour. Freezing of the tube took place almost immediately. The temperature was taken every ten minutes and found to vary between −10° and −17° C. Upon removal from the freezing medium the eggs were placed at room temperature (23° C.) and allowed to thaw. Time required for thawing: 30 minutes. Motile miracidia were commonly found inside the eggs at this time. Hatching took place normally from time to time as rapidly as in the control.

Exp. 4. Washed eggs were frozen as in Exp. 3., except that they were allowed to thaw at room temperature (24° C.) immediately on reaching the freezing point. Observation from time to time showed viable larvae hatching as rapidly as in the control.

Exps. 5-11. Eggs were washed and frozen as in Exp. 3, and were kept at freezing temperatures for the following periods of time: 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 18 hours. At the end of the respective time limits the media were allowed to melt at room temperature (23° C.) and examined from time to time. The ova were all found to be non-viable, the miracidia being dead, with large quantities of mucoid material extruded from their digestive glands. On mechanical expression from the shell, the larvae were oval in shape and non-motile, while the cytoplasm was milky in color.

Exp. 12. Semi-solid feces and blood, containing viable eggs, were frozen for one hour, then allowed to thaw and washed. The eggs were then placed at room temperature and examined from time to time. The larvae were all found to be dead.

Exp. 13. Semi-solid feces and blood, containing viable eggs, were heated to 43° C. for two hours, then frozen for one hour, thawed and washed. Eggs were examined from time to time and found to be all non-viable.

Series B.

Exp. 1. Eggs were washed and kept at 43° C. for one hour. They were then removed to room temperature and examined from time to time. Hatching was normal.

Exp. 2. Eggs were washed and kept at 45° C. for one hour, then removed to room temperature and examined from time to time. The larvae were living, but without sufficient vitality to hatch.

Exp. 3. Eggs were washed and kept at 47° C. for one hour, then removed to room temperature and examined. The shape of the miracidia was normal, as were the several body structures, but the larvae were all dead and the protoplasm was becoming milky.

These two series of experiments indicate certain definite conditions of temperature under which hatching can take place, and certain lower limits within which the developed miracidia may live unharmed and later hatch normally. Furthermore, a brief period (one hour or less) of excessive cold (–10° to –17° C.) seems to produce no injury, although the time limit of such excessive cold lies under two hours. These data were obtained from washed eggs in hypotonic media. In semi-solid feces, unwashed (Exp. 12), the same conditions do not hold, for in this state the larvae are killed in less than one-hour's freezing. In winter mature eggs under extreme conditions in endemic areas would soon become non-viable in small fecal dumps, but if deposited in canal water would sink to the bottom of the canal and hatch, or, if the water was too cold (4° C.), they would remain viable for some time and probably hatch at a later period. Although freezing of the surface of small bodies of water occurs in endemic areas in China it is highly probable that this would not affect eggs which had been previously deposited in the water and had sunk to the bottom.

As for the upper limits of temperature at which hatching may take place, it seems certain that this limit (43° C.) is safely above the temperatures of bodies of water in infected areas in which the eggs ordinarily develop.

(*c*) *Chemical constituents of the medium.*—We have tried only a few of these. The larva lives in tap water (slightly alkaline) and distilled water equally well. Normal saline and Locke's solution cause shrinkage of the egg after considerable time. Calcium chloride, in solutions heavy enough to bring the eggs to the top of the medium (sp. g. 1050 or over), causes immediate shrinkage and death of the larva. Cresyl blue and Nile blue sulphate, when introduced in weak dilutions with swimming miracidia, are noticeably toxic. Potassium alum (1 per cent.) causes immediate shrinkage of egg and larva. These may be partly physical reactions, but are possibly also in part chemical in their nature. Miyagawa (1916: 467–469) has found hydrochloric acid and potassium acetate toxic in all amounts of 0.05 per cent. and over, and phenol toxic in all percentages of 0.1 or more. These data correspond to those of Looss and others on bilharzia miracidia, where 0.05 per cent. hydrochloric acid immediately kills the larvae.

Three doses of sodium-antimony-tartrate which were administered intravenously to the host, in 2 per cent. solution, caused death of the eggs in the gut, although the worms were not noticeably affected by the drug. This will be discussed in greater detail in a later paper of this series.

A factor frequently determining the viability of the egg is the acidity of the medium. In a number of stools, with low acid content and no free acid, viable eggs were invariably found. In other stools which had developed a moderate acidity (30–36 c.c. *n*/10 sodium hydroxide titration) the larvae were dead. This usually occurred in a pasty stool containing much starch, and was particularly the case in stools sent us from a distance for examination. This factor is closely bound up with fermentation.

(*d*) *Fermenting agents.*—These are usually bacteria or yeasts in the stool which give rise to a yeasty sourness in the specimen and rapidly cause the death of the larvae. *We found that by washing the eggs several times, immediately after the motion was passed, the action of these organisms could be reduced to a minimum, and hatching allowed to take its normal course. We regard this as the most important element entering into the hatching of a mature egg under normal conditions, for with fermenting organisms present hatching could be effected only occasionally, while by eliminating these organisms by frequent washings hatching was readily effected.* This is exactly the method which operates in nature, when feces are deposited in water or are washed by rains.

The time element involved in hatching varies with the other factors concerned. A mature normal miracidium hatches readily when the tonicity of the medium is appreciably lowered. With a hypertonic medium the process is entirely inhibited, and sooner or later the larva dies. Since the time element is reduced to a minimum by the conjunction of optimum conditions (both external and internal) for hatching, and is lengthened whenever any one of these elements departs from the norm, it seems probable that three or four days is the maximum length of time possible under conditions prevailing in endemic centers for the larvae of *S. japonicum* to remain viable in fecal dumps, except where prolonged periods of cold weather prevail. This phase of the problem will receive consideration in a later paper of this series.

Since the movement of the worm within the egg shell undoubtedly has an appreciable effect on the rupture of the shell, agitation of the medium is evidently an aid to such a process. Yet this is probably not a normal course under field conditions and does not fundamentally concern us.

Hatching.

Once prepared for, the process of hatching is a simple one. The shell membrane splits along the line of least resistance, which from our observation is along the long axis of the egg on the side opposite the spine. This allows the shell to retract as it opens, and permits the mira-

cidium to escape along with the mucoid mass with which it is surrounded. If the larva becomes tangled within the shell, considerable muscular effort may be required to effect escape. In any event the bodily movement, both before and after hatching, precedes the ciliary one, although in a mature miracidium motility of the cilia is begun very shortly after the miracidium hatches, and in the case of late hatching possibly within the egg. This ciliary movement is of two types and is accomplished by two distinct groups of cilia. The anterior group (Figs. 9, 11) takes up its duty first, actually freeing the organism from its entanglements. When once free from debris the posterior group takes up movement, the waves of motion proceeding steadily from front to back of the series, until the whole set is in motion. The mucoid envelope in which the miracidium is frequently found immediately after the rupture of the shell is apparently only an accidental capsule which hinders rather than aids the larva in taking up its free-swimming existence. The normal method of emergence of the larva from the shell is head-on. Backing out usually results in rupture of the ectoderm.

The free-swimming miracidium.

The miracidium, on emerging from the egg-shell on the substratum, takes up a straight-forward movement, causing the larva to elongate, so that its length is five to six times its transverse diameter, a shape which cannot be photographed because of the rapidity of movement. The shape at this stage is very much like that of a rapidly moving paramecium, although the movement is a straightforward drive with dorsal side uppermost, rather than a corkscrew progression. In order to understand the actual free-swimming activity of the organism a single specimen recently hatched was placed in a drop of water in a watch-glass and its movements observed for two minutes with a binocular microscope. The accompanying sketch (Textfigure *B*) shows the path of the miracidium during that interval. Analysis of the course shows (1) that the elementary movement is a straightforward drive; (2) that the edge of the drop of water or any small obstacle in its path diverts it in an oblique direction; (3) that this direction is sometimes to the left and sometimes to the right of the previous path; and (4) that the complete reversal of direction is effected by the turn-table method, the number of degrees to the turn depending on the angle of incidence at which the organism strikes the obstruction. This same miracidium, temporarily at rest, is only 2 to 3 times as long as its broadest diameter.

Soon after the miracidium has hatched, in the event that it finds itself in clean water, it leaves the substratum and ascends to the top,

remaining within a few millimeters of the surface during the full time of its *infective stage*, where it swims around in the course just described. In dirty water, however, it probably swims deep. This infective period lasts from 60 to 72 hours. At the end of this time it enters upon a stage which may be termed the *post-infective stage*. During this decadent period the larva tends to become elliptical to barrel-shaped and to assume

TEXTFIGURE B. Movements of a miracidium of *Schistosoma japonicum* through a drop of water during a period of two minutes.

at times a slow uncertain infusorian or even zigzag movement. During this stage, partly due to internal changes and partly because of the decreased movement, the body is not more than three times as long as broad and lacks the vitality to penetrate the molluscan host. When this stage is reached the larva soon dies.

The miracidium seems to react neutrally to rheotaxis, but is probably positively phototactic, as indicated by the flocking of the larvae to the surface of the water and to the face of the light during the infective stage. It is negatively thigmotactic, as indicated by the reaction to obstacles met in its path.

Hatching of the eggs of one batch is not synchronous, but takes place over a period of two to four days. About one-half the batch hatch a few hours after washing the feces, while the remainder come out singly at irregular intervals. This is probably due to a slight difference in maturity, but may be caused by differences in the limit of elacticity of the shell.

Description of the mature miracidium.—(Figs. 9, 11.) In order to get accurate measurements of the miracidium one must resort to fixed material, since the rapid movement of the organism through the water makes measurement of it an impossibility. Miracidia of the typical infective stage and of the post-infective stage were killed in hot 10 per cent. formalin and in cold Schaudinn's fluid and stained in a modified hematoxylin. It was found that the range of the former series was 78 to 120 μ in length by 30 to 40 μ in breadth, with mean averages at 97 μ and 35 μ respectively. In the post-infective specimens, although the length measurements were practically identical with those of the former series, the breadth ranged much higher, namely about 52 μ. Observation of these specimens and measurement of internal organs show that, while the cross-section of the larva is circular at the infective stage, it becomes oval by being flattened out laterally as it approaches the post-infective period. The ratios of these dimensions may be expressed as (1) $\frac{\text{length}}{3}$ = breadth, and (2) $\frac{\text{length}}{2}$ = breadth, or in other words the breadth increases by a half as the free-swimming period of life approaches its end. However, this broadening is compensated by a flattening of the miracidium.

The mature miracidium is a free-swimming organism adapted to fresh-water, and in order to meet the needs of this environment it is provided with epidermal cilia. Grossly speaking, they resemble the ciliary hairs of protoplasm found on the infusorian. In fact, a careful examination of living specimens, paralyzed by staining with vital dyes, and of sections, containing fixed specimens, shows them to arise from a small basal spherule in the epidermal cell, similar to the basal ciliary structure of paramecium and possibly functionally the same as the blepharoplast of the protozoan, possibly communicating with the base of the nerve fibrils. If such is the case it is easy to explain the synchrony of movement in the cilia.

Authors who have studied schistosome miracidia have described and figured the organism as a holotrichous type, that is, one in which the cilia are all of one kind. As a matter of fact, (Fig. 11; Photomicrographs 11, 12) there is an anterior group of these cilia which is different from the posterior group topographically, structurally and functionally. Careful observation of living specimens, stained with cresyl blue or neutral red, shows that the region between the openings of the lateral gland cells laterally and the openings of the pair of head gland cells anteriorly is covered with a series of densely arranged cilia, which are noticeably long laterally, but become gradually smaller anteriad. The

most posterior of these are noticeably thickened basally, while the cilium just in front of the pores of each cluster of lateral ducts is uniquely thickened basally, is stiff and has the shape of a sickle, with a distinct handle at the base. This cilium is seen not only in vitally stained miracidia, but is also found in sections cut in an exact frontal plane (Fig. 12). It is this anterior group of cilia which initiates the swimming process as the miracidium first comes out of the shell; it is likewise this group which remains motile in senile and moribund specimens after the posterior cilia have failed to function.

The posterior group consists of long delicate protoplasmic hairs, spaced some distance from each other and performing the ordinary swimming functions. There is no differentiated crown of cilia in this species of miracidium, just anterior to the excretory pores, such as one of us (E. C. F.) has observed in the miracidia of *Schistosoma haematobium*.

Thus the organism, as a free-swimming individual, is well equipped for the rapid course which it takes through the water. Its epidermal differentiation is thus of more than passing interest.

The gut consists of a short solid pocket of tissue at the anterior end of the larva. Buried deeply in the granular protoplasm of this undifferentiated organ are four nuclei. It is apparent, both from a study of the structure and from observation of the motile larva, that the digestive tract is either primitive or vestigial, for it never comes to function.

Just laterad to the gut are the two cephalic glands. They are pyriform bodies with attenuate necks, and extend through the anterior third of the miracidium. They contain a prominent vesicular nucleus, and are densely packed with heavy granules which stain deeply with neutral red and eosin. They are oxyphilic in reaction. Posterior to these glands is a mass which has been described by authors as the brain mass. It fails to stain with neutral dyes, and only the small nuclei stain with hematoxylin (Photomicrographs 13, 14). Looss (1896: 165, pl. 11, fig. 113) shows nerve fibres extending out from this mass in the miracidium of *Schistosoma haematobium*, but Cort (1919: 512) failed to find such fibres in the larvae of *S. mansoni* and *S. japonicum*. Holcomb (1907: 68) regarded this mass, in the case of the miracidium of *S. mansoni*, as a stomach. None of these interpretations *per se* seem to satisfy the case, particularly since there are definite "duct" pores, lateral to this body, figured by Cort (1919a: Figs. 2, 6), with "internal relations not clear." Cort further observed that "extrusion from them of the oil globules was observed both in *S. japonicum* and *S. mansoni*."

Under favorable conditions these ducts (really lateral ducts)

are seen to be a multiple cluster which, when traced mesad, end in a central viscous mass. Moreover, we have traced drops of mucoid secretion (not "oil globules" as Cort supposed) from their inception in the center of the mass throughout the length of the duct to their deposition at the side of the larva (Fig. 11; Photomicrograph 12). We have come to the conclusion, therefore, that this complex consists of a dense mass of secretory cells, apparently basophilic in reaction and mucoid in nature, which empty their products through the lateral ducts just described. These glands should be termed *lateral glands*. This same type of gland complex is even more conspicuous in the miracidia of *S. haematobium* (E. C. F.). We have observed, likewise, a round group of true nerve ganglia with prominent cells on the side of the miracidium opposite the mucoid cell complex. (Figs. 9, 11.)

Sewell (1922: 286–289) offers an extremely interesting theory regarding the lateral ducts of the miracidia of *Schistosoma haematobium* and of *Cercaria indica* XV. He is impressed with the possiblilty of their connection with the six epidermal excretory canals which he has observed in the latter miracidia. He believed that the "anterior ducts" which he observed, were non-functional and were only blind excretory ceca. Like other observers of these ducts he has failed to trace them inward beyond the anterior flame-cells. Since we have commonly observed mucoid to be poured out from these lateral duct pores in both the miracidia of *S. japonicum* and *S. haematobium*, and have been fortunate enough to have seen this process in several instances, from the inception of the mucoid drop in the center of the cell mass above the nerve center, we feel that we have solved the function of these lateral ducts ("anterior ducts"), namely a secretory one.

As regards the neural mass, this can be demonstrated better in freshly hatched miracidia stained with neutral red than in preserved specimens. Under a favorable combination of staining and light the central nerve mass will be seen as a round mass of cells below the mucoid glands connecting with the lateral ducts. The cells of this clump are compact and stain slightly with neutral red. They are round in shape, contain a small round nucleus and minute chromidia in the cytoplasm. Furthermore, from this mass we have seen on two occasions definite sub-epithelial cords, six in number, two dorsal, two lateral and two ventral, with two transverse commissures belting the system (Fig. 11). The longitudinal elements extend both anterior and posterior to the central neural mass and are composed of both fibres and cells of irregular outline. It seems highly probable, therefore, from their relation to the central nerve mass that they represent the three anterior

and posterior pairs of nerve trunks common in the adult schistosome. These may be the cords which Sewell (l.c.) has regarded as epithelial excretory tubules, since the number and distribution correspond almost part for part.

The excretory system of the miracidium of *Schistosoma japonicum* has been described by Cort (1919: 518). There are paired flame-cells on each side of the body, one anterior and one posterior, leading out through capillaries into a common collecting tube. This communicates with the outside by means of a pore, situated in the posterior third of the body.

The flat mesodermal tissue, lining the body cavity, consists in part of muscle elements, but for the most part is made up of germinal epithelium. Germ cells are derived from it in the posterior two thirds of the body. These may be few in number, as Cort has observed them (1919*a*: 518), or may be very numerous, amounting in some instances to more than one hundred germ balls, free in the body cavity. In no case have we seen these germ balls further advanced than the one-cell stage. These may degenerate in the body cavity and produce irregularly shaped mucoid masses (Figs. 9, 10).

The miracidium as an organism invading the snail.—Soon after the miracidium is set free in the water it mounts to the surface, where it swims about in the sub-surface region as previously described, provided this tropic mechanism is not disturbed by the presence in this area of a mollusc of the genus Katayama or a closely related form. Experimental proof of the relation of the mollusc to the invasion-mechanism and the reaction of the miracidium to the mollusc was obtained by us in several ways.

1. *Specifiity of the host.*—In a previous year's experimentation we subjected the ordinary snails of North China, *Vivipara quadrata* and *Lymnaea plicatula* to water in which healthy miracidia were swarming, and in no instance was a positive taxis obtained. In the present series of experiments free-swimming miracidia, hatched from (*a*) eggs from experimental dogs infected with Japanese cercariae, and (*b*) others, hatched from eggs from a Wuchang patient (Chinese) under observation in the Peking Union Medical College Hospital, were placed separately in water together with specimens of *Katayama nosophora* from Kyushu Province, Japan, and their movements were observed. The behavior of these miracidia was the same as previously noted in the description of the free-swimming condition, except in the event of the miracidium coming within a few millimeters range of the snail. In the latter instance the miracidium became positively tactic to the

snail, swimming with full speed toward, attacking the body of the animal at the first place available. In many instances the miracidium secured a hold on first attack, boring its way into the body within a short time. In other cases it was not successful, being repulsed, perhaps, by the movement of the mollusc or the impregnability of the area attacked. It can be definitely stated, however, that the miracidium, once having come within the area of the mollusc to which it tactically responds, is not satisfied until it has invaded the animal. Experiments showed also that the area behind the snail, where a thin streak of mucus, secreted by the snail, was left, was also an area of attraction for the miracidium. It seems highly probable, therefore, that the stimulus is a chemotactic one, and that the source of the stimulus is the mucous secretion of the mollusc. If this is the case, *specificity of mollusc host may become a problem of specificity of mucous secreted by the mollusc.*

It was found that the miracidia from Japanese and Chinese material responded equally well to the stimulus of the snail *Katayama nosophora* from Kyushu Province, Japan. This brought us to the conclusion that the mollusc host of the Chinese variety, then unknown to us, must be the same or a closely related species.

2. *Number of miracidia attacking the mollusc.*—It was apparent from observation at the time of attack, and later on in sections of the infected snails, that many miracidia might attack and invade the organism at once. In a single exposure, practically all of the viable miracidia in a given container disappear within the body or shell of the snails subjected to infection. However, we have continued the process to a point, where on subsequent exposures none or very few of the miracidia enter the snail, most of the group remaining behind after removal of the mollusc. This would seem to indicate a certain maximum infectability on the part of the mollusc. However, if this is the case it has certain time limits, for after a period of several days the same mollusc may be readily reinfected, as determined by the disappearance of the miracidia from the infective medium with the removal of the snail. Likewise, molluscs, having carried an infection to the point where the cercaria is maturing, may be reinfected. This has been demonstrated in sections of the mollusc containing two clearly defined infections. (Photomicrograph 21.)

3. *Point of attack and penetration.*—To determine this point thirty snails of one series were each placed in a drop of water containing a single miracidium and the following data secured: (1) length of time before the miracidium first showed a tactic response to the snail; (2)

movements of the miracidium during attack; (3) point of entrance into the snail, and (4) examination of water for miracidium one half hour afterward upon removal of mollusc. These data are set down in the accompanying Table I.

This experiment shows clearly that the most exposed and accessible portions of the body are the ones first attacked and presumably the ones penetrated in most cases, although the presence of some larvae in the water, after removal of the snails, gave evidence that the initial attack was not necessarily successful. There is a further likelihood that some larvae were taken into the mouth of the snail and triturated by

TABLE I.

Data on attack and penetration of single miracidia of Schistosoma japonicum, each into separate snails of the species Katayama nosophora (Kyushu material).

Experiment No.	Time required for first stimulus.	Movements and point of penetration.	Examination of water after removal of snail.
1.....	5 minutes	Boring behind eye; then free, then disappearing under shell.	+
2.....	Immediately	Bored into foot.	−
3.....	2 minutes	Penetration almost immediate, bored into head.	−
4.....	Immediately	Bored into head between eyes.	−
5.....	1 minute	Bored under head near foot.	−
6.....	6 minutes	Disappeared under foot.	−
7.....	4 minutes	Disappeared under foot.	−
8.....	12 minutes	Penetrated foot.	−
9.....	2 minutes	Penetrated foot.	−
10.....	5 minutes	Penetrated foot.	−
11.....	1 minute	Swam into mantle cavity.	−
12.....	2 minutes	Sucked up into mantle cavity.	−
13.....	2 minutes	Disappeared within shell.	−
14.....	30 seconds	Bored into foot.	−
15.....	2 minutes	Bored into foot.	−
16.....	1 minute	Attacked head.	+
17.....	1 minute	Swam under opercular opening.	−

TABLE I.—*Continued.*

Experiment no.	Time required for first stimulus.	Movements and point of penetration.	Examination of water after removal of snail.
18.....	2 minutes	Bored into foot.	+
19.....	2 minutes	Bored into foot.	−
20.....	10 seconds	Disappeared under anterior part of foot.	+
21.....	3 minutes	Bored into "neck."	+
22.....	1 minute	Disappeared under foot.	+
23.....	1½ minutes	Disappeared under foot.	−
24.....	1 minute	Disappeared under foot.	−
25.....	10 seconds	Swam into opercular opening.	−
26.....	1 minute	Bored into neck.	−
27.....	10 seconds	Disappeared under foot.	+
28.....	2 minutes (1st attack); 12 minutes free; 1 minute (2nd attack)	Bored under mouth.	−
29.....	1 minute	Disappeared within mantle cavity.	−
30.....	1½ minutes	Bored into foot.	−
	Average time for 1st attempt: 2 minutes 46 seconds	*Summary for points of penetration.*	*Examination of medium.*
		Foot..... 9	Water +..... 7
		Head and neck..... 8	Water −.....23
		Mantle cavity..... 6	—
		Disappeared within or under body.... 7	30
		—	Maximum percentage of attack (and penetration?) indicated 76.6.
		Total.....30	

the radula, while still others may have temporarily gained hold of the outside of the snail and later swam out again into the water. There is likewise the possibility of trauma or senescence during the period of attack. The latter is not improbable, since the larva uses up its energy at a tremendous rate, and has no reserve on which to draw, until it reaches a source of new nourishment within the snail. The adaptation is, therefore, a very precise one and the mechanism a delicate one, with little provision for chance miscarriage.

In subjecting snails to infection with large numbers of miracidia, the same phenomenon was noted as in single instances, namely, that the head and foot were the most evident centers of attack, the areas at the bases of the tentacles near the eyes being attacked particularly often. But at times the larvae even attached themselves to the shell and attempted penetration.

Another series of experiments was performed to determine (1) the level of the water, where the maximum numbers of viable miracidia congregated, and (2) what bearing this might have to infection. Two graduate cylinders of 250 c.c. each were filled to a height of 19.5 cm. with tap water containing large numbers of viable miracidia. The larvae immediately concentrated in the top 3 or 4 cm. of water, while the greater share of these was found in the top cm. of water. Several snails were placed in the bottom of the first cylinder and continuous observations made for 60 minutes. The snails soon began crawling up the side of the cylinder. After 27 minutes the first snail reached the level of the lowest miracidium, which was at 14 cm. water height. This was approximately the same level as the lowest miracidia in the control cylinder.

At the end of 33 minutes the miracidia were observed to be swimming around at the same level as at the beginning of the experiment. After a lapse of 55 minutes eight snails had reached the top of the water and were being attacked. Ten minutes later a total of twelve snails had reached the top and crawled out, while others were near the top and were being attacked. These were all knocked down into the water and allowed to crawl up the cylinder again. Attack, this second time, occurred as before, namely only in the top level of water. Meanwhile most of the miracidia in this cylinder had penetrated snails so that the majority of the free larvae were gone. The experiment was repeated several times with the same results: that the larvae were not stimulated to alter their positions from the top stratum of water by the movements of the snails crawling up from below; but that they attacked and soon penetrated the snail when once the host arrived at the normal water level for the miracidia. It is, then, a prime consideration, that the snail, to be penetrated by the miracidia of *S. japonicum*, should have the habit of crawling to the surface of the water in order to meet the optimum requirements for infection. If the snail is above the waterline, sudden rise of the water might influence the period of infectivity. But even when such high water conditions do not prevail it seems probable that the snails periodically return to the water of their own accord and thereby give opportunity for the discharge of mature cercariae.

B. The developmental cycle of *Schistosoma japonicum* within the mollusc host.

The miracidium penetrates the snail to which it is physiologically adapted and after a period of time, stated by authors to be from seven to nine weeks, fork-tailed cercariae are set free from the mollusc. It is the purpose of this portion of the paper to set down our observations on the intra-molluscan phase of this life cycle.

For material on which to ascertain the needed data one hundred specimens of *Katayama nosophora* from Kyushu Province, Japan, were submitted to infection with active miracidia of *Schistosoma japonicum* hatched from eggs from the feces of a Chinese patient (Wuchang case heretofore mentioned). Of this number two snails were killed every other day, beginning on the third day. We had previously ascertained by dissection of several thousand specimens that the infective incidence of the snails used was considerably less than one per cent., so that the possibility of confusing old infections with new was slight. As a matter of fact one such double-infection was found in our series and was detected without difficulty. All of the snails used in this series of experiments were also known to have been free from contact with miracidia for several weeks. To this series was added later, for the sake of completeness, a group of five specimens, killed one-half hour after submission to infection with miracidium from a Soochow source, and others of Japanese infection containing mature or maturing cercariae. The main series was continued through the forty-seventh day, at the end of which time the snails were exhausted, due in part to death from a fungus. It is possible, likewise, that some of the snails may have died from a too heavy infection with the miracidia or from starvation.

The specimens in the series were fixed in hot 10 per cent. formol, after the shells had been cracked. They were then removed from their shells and sectioned 5 to 7 μ in thickness. Examination of these sections provided the necessary information for tracing the developmental cycle in the snail.

Of the forty-six snails sectioned, in the main series, only five were found to be uninfected, while a sixth had a heavy infection from a previous natural exposure in Japan as well as the laboratory infection. This left forty-one of the group examined which had been infected from our material. In five specimens of the infected group only one worm each was found, while in the remainder the numbers ranged from two to several dozen of the original generation. There is, therefore, every

evidence to show that *when the mollusc to which the larva is adapted or adaptable is submitted to a heavy infection, a heavy infection actually occurs in the mollusc.*

The progressive history can be traced from a study of Table II. First of all, the miracidium penetrates the snail, at the point of contact, by a head-on boring motion. This is undoubtedly aided by the proteolytic enzymes of the head glands. We have previously shown that the places most frequently attacked are those most accessible, namely, the head and foot. Various authors, including Leuckart (1901: 265), have suggested that although such penetration has been observed by them, the fate of the larva was probably premature since its development within a solid organ like the foot was very unlikely. Under such a theory one would expect to find early stages of the larva in these organs during the early days of the infection, but a progressive degeneration or atrophy of the worm later on. We believe we have adequate evidence for stating that such a theory is based on insufficient evidence. In the first place the foot and the solid portions of the head are not entirely solid muscular elements, but contain mesenchymatous tissue and lymph spaces in addition to the mucous glands of these areas. Perhaps it is the mucous secreted from these same regions which attracts so large a percentage of the total number of miracidia to penetrate these organs. In the second place, actual development of the worm in the midst of the deeper lying tissues of foot and head shows these tissues to be adequate to support life and growth of the worm and not to inhibit such growth.

Briefly stated, the history of *Schistosoma japonicum* within the snail is one involving lymph spaces, in which the worms are bathed in liquid nourishment. While certain of the miracidia get directly into the gill sac and thence are taken through the blood and finally into the lymph sinuses between the liver lobules, the majority do not reach this commonly described location of infection, or if they do, they arrive there at a late date, probably at the time when the second generation sporocysts erupt from the parent spore sac. In the latter instance the route is an indirect one, following the deeper lying lymph channels.

The direct route.—The masterly work of Leuckart (1901), on various life-histories, indicated clearly that the direct route of infection for the miracidium on entering the mollusc was first through the breathing pore into the mantle cavity, thence into the brood-chamber, where the rapid movement comes to an end due to the shedding of the ciliated epiderm. Leuckart (l.c., 265), states that a certain few of the

miracidia of *Fasciola hepatica* invade the foot or other heavy organs and that only occasionally does one such penetrate and metamorphose into a sporocyst. He believed the earlier movements of the larva to be a form of peristalsis. He concluded that the direct route through the mantle chamber, and thence into the blood was the method of practically all infections.

We have found that some of our material shows such stages of direct infection, although this portion is indeed small when compared with the other group of the series. The sequence of events may be described as follows. The miracidia first swim into the mantle cavity, where they are seen rapidly moving about in a fully opened snail. They attack the mantle-wall or the specialized gill region, effecting actual penetration more readily than at any other part of the snail (Photomicrograph 20). We have then found them invading the branchial vessels, thence reaching the heart and the aorta. Four days later such a route brings the larva into the inter-lobular lymph spaces surrounding the liver. The only other possibility, that of swimming against the afferent branchial stream, seems unlikely.

Further development in this route consists in differentiation of the larva into a first generation sporocyst, the intra-sporocyst development of a second generation of sporocysts, and a further development of cercarial larvae within the second generation sporocysts. We have found, furthermore, that the time for this development is not materially shortened by following the direct route in invading the region of final development.

The indirect route.—In our studies the majority of the miracidia entered the head and foot. While the progress of the larva along the direct route is surprisingly slow, that through the indirect route is notably rapid considering that the tissues are more difficult of penetration. Actual penetration through the head or foot epiderm occupies at most only a few minutes. It is then comparatively simple for the ciliated miracidium, still equipped with proteolytic ferments secreted by the head and lateral glands, to digest away mesenchymatous tissue, thus forming a space which soon becomes connected with the lymph system (Photomicrograph 16). On the second day two larvae were found in the head near the brain centers. Thence they apparently work backward in the lymph spaces surrounding the nervous centers of the animal, since they occur on the fifth and seventh days in considerable numbers between the neural mass and the esophagus as far back as the radular pocket. In the next four to six days they wander backward into the lymph spaces around the salivary glands.

TABLE II.

Course and development of larvae of Schistosoma japonicum from Chinese patient within the Japanese snail (Katayama nosophora), collected in Kyushu Province, Japan.

Day.	Location in snail.	Number found.	Stage of development.
1st day*, as of March 14.	*A.* Lying in artificial lymph space in parenchyma of head.	1	Similar to free-swimming miracidium.
	B. In mantle cavity, penetrating gill filaments.	2	Similar to free-swimming miracidium.
3rd day*, as of March 16.	*A.* Lying in lymph space in head.	2	First degenerative changes occurring; ciliated epiderm gone.
	B. In outer gill chamber.	1	
5th day, March 18.	*A.* Between inner mantle and brain.	1	Basophil glands still present.
	B. Between ectoderm and right buccal ganglion.	1	
7th day, March 20.	*A.* i. Within ventricle.	1	Elongating; basophil glands gone.
	ii. Anterior aorta near ventricle.	1	Elongating; oxyphilic glands still seen.
	iii. Posterior aorta near ventricle.	1	Elongating.
	iv. Between esophagus and cerebral ganglion up to radular sac.	10	Elongating; proliferating germ balls.
	v. Lymph space near gills.	1	
	vi. Between esophagus and right salivary gland.	2	
	vii. Above right cerebral ganglion.	2	
	B.	0	Apparently uninfected.
9th day, March 22.	*A.* Lymph space above right optic nerve.	2	Losing differentiating characters of miracidia; elongating.
	B. i. Foot, deep lying near pedal ganglion.	2	Elongate.
	ii. Lymph space near anterior esophagus.	1	

* Indicates later infections of the day concerned, placed in this series for the sake of completeness.

TABLE II.—*Continued.*

Day.	Location in snail.	Number found.	Stage of development.
11th day, March 24.	*A.* Lymph spaces near salivary gland.	2	Elongate sac.
	B. i. Lymph spaces near salivary gland.	1	
	ii. Lymph spaces near anterior esophagus.	1	
	iii. Lymph spaces near liver.	1	Elongate; division of germ balls into 2 and 4 cells.
13th day, March 26.	*A.* i. In nephridium.	1	65 μ long x 54 μ.
	ii. Foot, deep lying.	1	80 μ wide x 110 long.
	iii. Lymph space in nephridia.	1	
	B. i. Lymph spaces around anterior esophagus near cerebral ganglia.	8	All with enlarged germ balls, dividing, 2 to 8 cells.
	ii. Lymph space above left eye.	1	
	iii. Lymph space between brain and mesoderm, right side.	1	
	iv. Same left side.	2	
	v. Mantle over salivary glands.	1	
	vi. Foot.	1	
15th day, March 28,	*A.* i. Tentacles over eye.	2	Morula stage of germ ball.
	ii. Lymph space under eye.	3	
	iii. Mantle over anterior esophagus.	1	
	iv. Foot, deep lying.	2	
	v. Lymph channel between crop and nephridia.	1	
	B. i. Gills.	1	
	ii. Lymph spaces between salivary glands and anterior esophagus.	6	
	iii. Base of tentacles.	2	
	iv. Lymph spaces near cerebral ganglia.	4	

TABLE II.—*Continued.*

Day.	Location in snail.	Number found.	Stage of development.
17th day, March 30.	*A.* Foot.	2	
	B. Lymph channels in liver and spermary.	many	First generation sporocyst; also mature cercariae of previous infection.
19th day, April 1.	*A.* i. Lymph channels between foot and mantle.	3	Elongate larvae, ca. 25 x 100 μ.
	ii. In nephridium.	2	
	iii. Lymph spaces between liver and ovary.	3	
	iv. Lymph spaces between mantle and muscles of head.	many	
	v. Foot.	3	
	vi. Lymph spaces between mantle and gills.	2	
	vii. Lymph spaces between mantle and brain.	many	
	viii. Lymph spaces over foot.	many	
	B. Lymph channel over salivary glands.	1	
21st day, April 3.	*A.* i. Head near left eye.	1	Morula stage or secondary sporocysts.
	ii. Foot near gills.	1	
	iii. Mantle cavity near esophagus.	1	
	B. i. Head above left eye.	1	
	ii. Lymph space near esophagus.	1	
	iii. Lymph space between gut and liver.	1	
23rd day, April 5.	*A.* Lymph space near spermary.	1	Morula stage.
	B. i. In left salivary gland.	1	Few in morula stage.
	ii. In gill.	2	Many in morula stage.

TABLE II.—*Continued.*

Day.	Location in snail.	Number found.	Stage of development.
25th day, April 7.	*A*. i. Lymph space under tentacles.	2	Few morulae.
	ii. Mantle cavity near gills.	3	Elongating.
	iii. Spermary.	2	Many germ balls of secondary sporocysts, with body cavity, elongate in shape.
	iv. Imbedded in foot.	6	
	v. Lymph spaces in liver.	many	
	vi. Mantle cavity near liver.	1	
	vii. In parenchyma of head.	1	Slightly behind other regions in development.
	B.	0	
27th day, April 9.	*A*. Parenchyma of head.	3	Many small secondary sporocysts, free, immature; germ balls within.
	B. i. Parenchyma of head.	many	
	ii. Lymph spaces next to gut near liver.	2	Immature first generation sporocysts.
29th day, April 11.	*A*. i. Parenchyma of head.	2	Large primary sporocysts (120 μ in diameter) with elongate secondary sporocysts.
	ii. Mantle fold above brain.	3	
	iii. Muscle of foot.	2	
	iv. Parenchyma near brain.	1	
	B. i. Lymph space in liver.	2	Secondary sporocysts, small elongate.
	ii. Lymph space above brain.	1	Primary sporocyst.
31st day, April 13.	*A*. i. Lymph space above brain.	10	Primary sporocyst.
	ii. Spermary.	1	Secondary sporocyst.
	iii. Lymph space in liver.	3	
	iv. In nerve near cephalic ganglion.	3	
	v. Parenchyma near left salivary gland.	2	Primary sporocyst.

TABLE II.—*Continued.*

Day.	Location in snail.	Number found.	Stage of development.
	B. i. Salivary gland.	1	Primary sporocyst; wall of mother cyst thick; second proliferation of germ balls.
	ii. Lymph space near eye.	1	
	iii. Lymph space near right optic nerve.	1	
	iv. Left tentacle.	1	
	v. Lymph sinus beneath brain.	2	
	vi. Lymph space between gut and left salivary gland.	1	
	vii. Mantle wall near mouth of shell.	2	
	viii. Lymph space in liver.	1	
33rd day, April 15.	*A.* i. Lymph space near right salivary gland.	1	Primary sporocyst (400 μ long).
	ii. Lymph space in foot.	1	
	iii. Lymph space above brain.	1	
	B. Lymph space in head near left tentacle.	2	Large primary sporocyst.
35th day, April 17.	*A.* i. Lymph space in head.	2	Large primary sporocyst, with secondary sporocyst 125 μ long x 20 μ in diameter.
	ii. Mantle fold near foot.	2	
	B. i. Lymph space in foot.	1	
	ii. Above right eye.	1	
	iii. Lymph space in liver.	1	Secondary sporocyst with cercaria germ balls.
	iv. In muscles near kidney.	1	Primary sporocyst.
	v. Mantle fold near tentacle.	1	
	vi. In foot.	1	
37th day, April 19.	*A.* i. Lymph space near salivary gland.	1	Primary sporocyst.
	ii. Lymph space between gut and liver.	2	
	B. Lymph space between gut and liver.	1	

TABLE II.—*Continued.*

Day.	Location in snail.	Number found.	Stage of development.
39th day, April 21.	*A.* i. Lymph space in liver.	6	Primary sporocysts with elongate secondary sporocysts.
	ii. In lymph space near brain.	1	
	iii. In liver spaces.	1	
	B. i. lymph spaces of head.	5	
	ii. Mantle fold near head.	1	
41st day, April 23.	*A.* i. Lymph spaces in liver.	many	Second generation sporocysts with morula stage of cercariae.
	ii. Lymph spaces in spermary.	many	
	B. i. Lymph space near gills.	2	Primary sporocyst with advance secondary sporocysts.
	ii. Lymph space in liver near gut.	1	
43rd day, April 25.	*A.* i. Lymph space in liver.	2	Secondary sporocysts free 200 x 20 μ to 250 x 20 u.
	ii. Lymph space in liver.	many	
	iii. Lymph space in spermary.	many	
	B. i. Lymph space in spermary.	1	Primary sporocyst with many advanced secondary sporocysts.
	ii. Lymph spaces in foot.	5	
	iii. Lymph spaces in liver.	many	Second generation sporocysts.
45th day, April 27.	*A.* Lymph spaces in liver.	many	Second generation sporocysts.
	B.	0	Apparently uninfected.
47th day, April 29.	*A.* i. Lymph spaces between ovary and liver, and	many	Second generation sporocysts.
	ii. Spermary and liver.	many	Second generation sporocysts 250 x 40 μ. contain cercaria with differentiating tails.
	B. i. As above in A.	many	
	ii. Mantle fold.	many	First generation sporocysts.
60th day,* as of May 12.	Lymph space between liver lobes.	many	Mature and maturing cercariae.

In the meanwhile they lose their differential characteristics as miracidia, with ecdysis or (more probably) atrophy of the ciliated epiderm, while first the basophilic glands and then the oxyphilic head glands disappear. At the same time they elongate into sacculate structures, while the proliferation of germ balls continues from the germinal epithelium. (Compare Leuckart's observation on growth of the larva of *Fasciola hepatica* between the third and fourteenth day (l.c., 265).)

On the thirteenth day some of the worms are found in the lymph space around the nephridia, although it is possible that any worm found in this region or further posteriad may have come in via the direct route. At this time the germ balls first show cleavage into 2-, 4-, and 8-cell stages (Fig. 13; Photomicrograph 21). However, some of the spore sacs which become more deeply imbedded in the muscular elements of head and foot have not been able to make as rapid a passage toward the liver organs, although they have grown equally rapidly. The surrounding tissues show evidence of enzymatic changes, with a disappearance of the muscular elements in many cases and either replacement with stringy connective tissue or complete absence of tissue. These data support the views, (1) that the worm is able to live and grow in the more muscular areas of the body of the snail, and (2) that possibly some digestive action takes place on the part of the worm, even after the secretory glands have disappeared. To all this the snail apparently can offer no resistance and probably dies in the event of an overwhelming infection. On the other hand, no specimen was examined in which the worm, *when once it had penetrated into the tissues of the host*, was unable to establish itself and grow normally.

The sporocysts in the looser lymph channels probably wander into the inter-hepatic lymph spaces by the end of the third week. Others are caught in the smaller foci and have to remain for a longer period. This delay lasts until the second generation sporocysts mature and break out of the parent sac, when they are able again to take up the migration. Stray individuals may even enter nerve elements. From the third week on, no matter in what location, the primary sporocysts become large in diameter (up to 120 μ), while the germ-balls within begin to elongate (Fig. 14; Photomicrographs 22, 23). As this takes place a second proliferation of germ-balls is seen to be taking place (Fig. 15; Photomicrograph 23).

From the fifth week on the larvae come more and more to lie within the lymph spaces of the liver and hermaphrodite glands (Photomicrographs 24, 25). The general movement toward this region is a natural

one, for it is without doubt the loosest tissue of the body, and allows for considerable addition in mass without appreciable distortion either of host or parasite tissues. The germ balls of the cercariae now appear within some of the most advanced secondary sporocysts. These latter are elongate and narrow, with measurements of 200 μ in length by 25 μ, in transverse diameter, and are thus in considerable contrast to first generation sporocysts.

As the developing secondary sporocysts concentrate in the distal lymph spaces and cercariae begin to develop, the mass of this region becomes considerable and tension results. Even infection from a single miracidium has been found to develop a progeny which distends the integument of the distal organs, while the result of the invasion of several miracidia after several weeks causes immediate rupture of the whole region on pricking with a needle.

While the development was proceeding in a natural way in our experimental material, at the end of seven weeks the cercariae were just beginning to elongate and were far from the mature stage. Comparison of this stage (Fig. 18) with the mature fork-tailed larvae (Fig. 20) indicates that considerable time would have to elapse before the free-swimming stage of the cercaria had arrived. This period of further growth and differentiation seems not less than two weeks beyond the seven weeks stage. In another comparable series this maturing of the cercariae was studied and found to be complete at the end of sixty days after infection (Figs. 19, 20; Photomicrographs 25, 26).

Pathology of the invaded tissues.

In a previous paper one of us (Faust, 1920) discussed the area of the liver follicles affected by the larval fluke and how this came about as the result of the migration of the larvae to these foci, namely, through lymph and connective tissue channels. We have no new observations to add here to the pathological histology of the liver cells, as described in that paper, but it does seem wise to emphasize the point particularly for this study, that the tunnelling through muscle parts and mesenchymatous tissue, preliminary to actually arriving at the seat of final maturity, in itself constitutes a serious pathological process. This is particularly true in view of the apparent ability of the worm to digest away the intervening tissue at a considerable rate, leaving, in some instances, wide spaces between solid tissues. Furthermore, the ultimate seat of infection is not only the liver interstices, but those of the adjacent spermary and ovary, which organs also suffer from the same chemical and physical injuries, as does the liver (l.c.). It is little

wonder, then, that many molluscs are reported as killed by heavy invasions of miracidia. The requirement for space and nourishment is so great in heavy infections that little is left of the liver and surrounding region after removal of the worms. The latter make up the greater mass of the mollusc and leave only a weak skeleton of the digestive organs of the host.

C. The cercaria stage of *Schistosoma japonicum.*

(Figs. 18 to 21; Photomicrographs 25 to 28.)

Historically speaking the adult *Schistosoma japonicum* was the first stage of the fluke to be observed and described. This was followed by the miracidium, which was thought, for several years, to be the direct infective stage of man and other mammals. Only after the experiments of several Japanese investigators with "infected water" and the complete life-history demonstrations of Miyairi and Suzuki (1913, 1914), Miyagawa (1913) and Leiper and Atkinson (1915), did the scientific world have proof that the Oriental schistosome had a cercarial stage, as do all other known digenetic trematodes, with parthenitic generations intercalated between the miracidium and the cercaria.

It is the purpose of this portion of the paper to describe the period in the life-history from the emergence of the cercaria from the snail to the entry of this larva into the definitive host.

While direct observation is practically impossible on the infected area of a living snail encased in the shell, it seems evident from microscopic observation of sections that the only organs of the mollusc where second generation sporocysts mature and produce viable cercariae, are the lymph spaces situated between the liver lobules and between the hermaphroditic organs. Moreover, the development within these spaces, even at the expense and shrinkage of the host tissues, produces an hypertrophy of the region with tension on the *tunica propria* of this portion of the host, so that by the time some of the cercariae are mature the slightest additional tension or the inevitable mechanical movement of the larvae within causes first a rupture of the sporocyst wall and then of the *tunica propria* itself. This probably accounts for the spontaneous emergence of swarms of cercariae from within the shell. If this were not a sufficient impulse for eruption, the secretory products of the cephalic glands of the mature cercariae are without doubt potential aids in dissolving the host tissues concerned. However, in the case of the cercariae of *Schistosoma japonicum* it seems probable that eruption takes place only when the snail is immersed in water or at the water level.

Textbooks, following the early investigations on the life-history of *Fasciola hepatica*, usually state that, if a convenient environment is not at hand, or the conditions for transfer are unfavorable, development of parthenitic generations within parthenita takes place over an indefinite period of time and involves several of these intercalated generations. It is probable that even in the case of *Fasciola hepatica* the continued proliferation of parthenitic generations does not occur. In the case of the human blood flukes no evidence has yet been adduced to show that more than two sporocyst generations occur. Under these circumstances great prolongation of the intra-molluscan phase of the life-history can obtain only in so far as certain miracidia follow the indirect route of invasion and mature later. When this later progeny matures and escapes, the last opportunity for infecting the definitive host presents itself. In some instances mature and immature cercariae are found within the same sporocyst. Yet we have found young and maturing cercariae in sections of snails which had not been discharging cercariae for many days.

The spontaneous emergence of the cercariae can be readily demonstrated with Katayama snails which have been exposed to viable miracidia two or more months prior to observation, and which have been out of water for some days preceding the experiment. The snails are placed in water, whereupon they show activity almost immediately. Sometime later (after a period of several minutes to one or several hours) the observer may see with the low power of the binocular dissecting microscope cercariae emerging from within the shell. At times they come singly, at times in groups of twos or threes. In all of our observations these cercariae have always emerged tail first, with the anchor-fluke movement first described for the cystocercous cercariae (Braun, 1891; Ward, 1916; and Faust, 1918). This is the same movement which we have observed this larva to make each time an actual swimming movement is performed.

Very soon after emerging from the snail the cercaria swims upward through the water and comes to rest beneath the surface film directly above the snail from which it erupted. It lies ventral-side up and attaches itself to the surface film by its ventral sucker. In this resting condition the body is contracted, with a ratio of breadth to length of about 4 to 5. The tail is also contracted and is usually coiled to one side or hanging down in the water. Groups of several hundred of these cercariae in the surface film microscopically resemble minute Collembolae.

Movement in the cercaria consists of four distinct types: (1) a

vibratory movement of the body with the ventral sucker as a pivot, initiated by the tail and commonly seen in individuals in the surface films; (2) the ordinary swimming movement, in which the tail furci serve as an anterior propellor; (3) a sinking movement, in which the entire body is elongate, but inactive and in which with head foremost the cercaria descends through the water; and (4) the "measuring-worm" movement, which the larva performs in the surface film or at the bottom of the medium, apparently equally well with or without the tail. During all of these movements the worm moves its ventral sucker much more noticeably than it does later within the mammalian host.

Structure of the cercaria of Schistosoma japonicum.

Miyagawa (1913) and Miyairi (1914) were the first investigators to describe the forked-tailed cercaria in the life cycle of the Japanese schistosome. They were followed by Ogata (1914), while the more detailed account of Miyairi and Suzuki (1914) was relatively diagnostic, although still not without errors in observation. While most of this proof rested on experimental evidence, Miyagawa (1913) compared the fork-tailed cercariae which he secured from Katayama snails with the young worms which he had previously obtained from the portal system of experimentally infected animals, and among other things noted the absence of a true pharynx in both.

It seems a fortunate circumstance, however, that the Japanese during these investigations did not encounter other species of mammalian schistosome cercariae, for their descriptions were neither morphologically accurate nor specific. If, for instance, the mixed infections of fork-tailed larvae which exist in endemic areas of blood fluke infection in Egypt, South Africa or India had been encountered, it seems probable that some years might have been necessary to obtain a clean-cut experimental proof of this phase of the life-history.

While the work of Leiper and Atkinson (1915) definitely differentiated the two generations of sporocysts involved, it failed to add anything to the knowledge of the structure of the cercaria. However, Cort (1919) presented a full description of the cercaria and placed this phase of the anatomy of the worm on a firm basis, so that other investigators could not only definitely differentiate this larva from the non-mammalian fork-tailed cercariae, but by specific structures could show it to be different from the closely related mammalian forms, *Schistosoma haematobium*, *S. mansoni*, *S. bovis*, *S. spindalis* and *S. indica* XXX (Faust, 1920, 1921; Manson-Bahr and Fairley, 1920; Soparkar, 1921; Sewell, 1919, 1922; Khalil, 1922, and

Bettencourt et da Silva, 1922). All of these numerous researches, when thoroughly analyzed, show (1) that this group is apharyngeal; (2) that for this group the excretory system is constant, i.e., it possesses two pairs of flame-cells for each side of the body, with the posterior element of the posterior pair extended into the caudal trunk; and (3) that although the cephalic glands have been at times inaccurately and inadequately observed and described they constitute, nevertheless, specific characters by which definite differentiation of the species may be made. Aside from Cort's failure to correlate the hollow boring spines with the cephalic gland ducts (1919: 501), which relationship was pointed out by Faust (1919) and later corroborated by Cort (1921), the detailed description of the cercaria of *Schistosoma japonicum* by Cort (l.c.) constitutes a thoroughly accurate account of the free-swimming larva, and corresponds in all details to our own observations, both on Japanese and Chinese specimens of the larva.

The body and tail are entirely covered with strong reversed spines, so that the animal is materially aided by them in the penetration of the definitive host. The size and absolute shape of external parts cannot be taken as an arbitrary diagnosis at any time, since these differ materially in different states of contraction and expansion, in different ages of maturity, and perhaps even more profoundly due to other factors now unknown. However, mature specimens average about 0.32 mm. in total length, and can be measured with some degree of success shortly after they emerge from the snail. Ten average mature living specimens from a batch of Japanese *Katayama nosophora* gave the following measurements:

TABLE III.

Measurements of ten average mature cercariae of S. japonicum from Katayama nosophora.

Total length.	Body (length and breadth).	Tail trunk (length).	Furci (length).
320 μ	112 x 40 μ	150 μ	50 μ
320 μ	120 x 50 μ	140 μ	50 μ
310 μ	120 x 50 μ	140 μ	56 μ
320 μ	100 x 54 μ	160 μ	70 μ
300 μ	120 x 40 μ	140 μ	60 μ
276 μ	140 x 46 μ	100 μ	40 μ
350 μ	140 x 44 μ	160 μ	60 μ
360 μ	150 x 40 μ	150 μ	70 μ
320 μ	120 x 50 μ	150 μ	60 μ
360 μ	140 x 46 μ	160 μ	70 μ

Perusal of these figures shows a certain average size to prevail. Experience in measuring proves to the investigator that the differences of measurements in individuals are due more usually to contraction or extension of parts than to actual size variation. This same statement applies even more to the oral and ventral suckers than to the large divisions of the body, so that measurement of these organs, either in living or preserved material, is not by any means an absolute criterion for specific variation.

The excretory system in the cercaria.

The excretory system of the mature cercaria of *Schistosoma japonicum* was first observed and figured by Miyairi (1914) and Miyairi and Suzuki (1914) (Japanese text), although it was not accurately described until Cort (1917) published his observations. Following this Faust (1919*a*) showed that *this system, as described for the cercaria of Schistosoma japonicum, was the simplest type known for the entire group of the schistosome larvae,* and that this, as a representative of the mammalian schistosome cercariae, stood at one end of an extensive and complex series of systems for the schistosomes. Later observations have confirmed this view. Meanwhile other investigators have shown that the cercariae of the related mammalian schistosomes, *Schistosoma haematobium* (Bettencourt et da Silva 1922), *S. mansoni* sp. inq. (Khalil 1922), and *Cercaria indica* XXX (Sewell 1919, 1922) have the same flame-cell formula as the cercaria of *S. japonicum,* while the observations of Soparkar (1921) on the cercaria of *Schistosoma spindalis* agree with those of the workers on other mammalian schistosome species, except for the addition of a supernumerary flame-cell in the posterior group (l.c., Pl. I. Fig. 3). In the light of our studies on the young schistosomulum of *S. japonicum* after invasion of the definitive host, this supernumerary cell may be explained as a precocious development, anticipating the time when the caudal flame-cell is pinched off along with the tail and a new unit is formed by the division of the anterior unit of this group (see Figs. 21–23), thus producing the original symmetry of the system. The excretory system of the mammalian schistosomes is then, as far as present knowledge indicates, not a specific system, but a generic one, with a common flame-cell formula for the cercarial stage of the entire group. It can be relied upon among other distinctions as a criterion to differentiate mammalian schistosome cercariae from the non-mammalian species. As other writers have shown, the formula is $2 + 2$ for each side of the body, or $2 \times (2 + 2)$ for the entire larva. Since the anterior and posterior elements are

balanced equivalents, the series for one side may be expressed as $\alpha' + \alpha''$.

In order to understand the methodical development of the excretory system in the cercaria of *Schistosoma japonicum*, (and this as a representative for the group), we have studied the excretory system in the developing cercariae still within the mother sporocysts. In the young germ-ball which has just become elongate (Fig. 18) there is for each side of the body a single tubule proceeding from a single flame-cell and opening through a small pore posteriad. With the increase in size of the body and the differentiation of a caudal element, these tubules elongate (Fig. 19), and a division of the elemental flame-cell into two results, with a consequent splitting of the tubule part way, so that the two flame-cells come to occupy anterior and posterior positions. These are the fundamental α' and α'' groups. Then with the differentiation of furcal elements to the tail the distal ends of the tubules are separated one from the other. Along with this (Fig. 20) a second division of flame-cells with splitting of the adjacent tubules takes place, so that four flame-cells result for each side of the body. One of these comes to lie in the proximal region of the tail. Following this the main tubules in the tail trunk become fused, so that only one tubule is found in this region of the mature cercaria, except that in the proximal region, just behind the excretory bladder, evidence of the primitive type is still preserved in the separation around the Island of Cort (Fig. 21, *i*). Thus the excretory system, as found in the mature cercaria, develops by a series of methodical steps, and becomes established in the stage found in the mature cercaria long before the external features of the worm have become differentiated and long before the larva becomes actively motile.

The post-cercarial stage of the excretory system of *S. japonicum* will be described in a later section of this paper.

The digestive system of the cercaria.

The oral opening in the cercaria of *S. japonicum* is a small pore, situated on the ventral side of the body, antero-mesad in position. It is some distance from the openings of the secretory ducts which are directed anteriad. The digestive system consists of a thin-walled capillary tube, which from a lateral view resembles a stretched-out letter "S." The main stem follows the longitudinal axis of the body, while the outer oral end bends ventrad and the inner blind end is directed dorsad. The tube extends only about two thirds of the distance to the ventral sucker. As it approaches its inner end it enlarges to form a blind pouch, which, at times of distension, shows a slight bifurcation.

This pouch usually contains a few small mucoid bodies, but it seems highly probable that they do not represent true food inclusions. During the free-swimming period the digestive system is probably entirely non-functional.

The secretory glands of the cercaria.

Just as the miracidium of *S. japonicum* has definite secretory glands for digesting away the tissues of the snail, in order that invasion may be accomplished, so is the cercaria provided with such a secretory apparatus for attacking and penetrating the tissues of the mammalian host. The organs here are of two types, and consist of (1) five pairs of similar glands, situated in the posterior half of the body, with conspicuous thick ducts leading to the anterior end of the body, and (2) a single pyriform gland in the head, dorsal to the digestive tube (Fig. 21). In conformity with Cort's terminology (1919), and in view of the microchemical reaction of these glands (Faust, 1921: 20) it seems wise to refer to them respectively as (1) cephalic glands and (2) head gland.

The cephalic glands are well described by Cort (1919: 500), who refers to them as "unicellular with large nuclei filling almost all of the posterior half of the body. (He) counted five of these glands on a side. The ducts from the cephalic glands pass forward in two groups ventrad to the central nervous system and digestive tract and enter the oral sucker, as described above. These glands are loose in texture, the bulk of each gland apparently consisting of secretory products, and are pushed into all sorts of shapes by changes in the shape of the body of the cercaria." Our observations on large numbers of cercariae are in accord with Cort's as to the constant number of these glands. In view of the difficulty in detecting the exact number in living specimens, it seems altogether probable that the smaller number figured by Miyairi and Suzuki (1914) and the larger number figured by Miyagawa (1916) are due to errors in observation. These glands are similar to one another in consistency and staining reaction throughout their existence, and are therefore similar to the cephalic glands in the cercaria of *S. haematobium* (Faust 1920, Bettencourt et da Silva 1922) in which three pairs of glands of similar structure and staining capacity have been described. On the other hand, these glands differ from the cephalic glands of the cercariae of *S. mansoni* (Venezuelan and South African specimens, described by Faust, 1920), *S. mansoni* (?) sp. inq. of Khalil (1922), *S. spindalis* (Soparkar, 1921, Pl. I. Fig. 2) and from the cephalic glands of *Cercaria indica* XXX (Sewell, 1919), in all of which species two types of cephalic glands have been observed. Moreover on careful study of various stages of maturity we have found that in the earlier

stages the glands are dense and mucoid in consistency, but that later stages show a series of staining reactions through neutrophilic to eosinophilic, the latter reaction being obtained only in mature cercariae of this species, either those which have spontaneously discharged from the snail or those which have reached maturity and still lie within the parent sporocyst. Furthermore, this type of content may be observed in the course of invasion of the definitive host as long as the glands are present. As careful observation of these glands becomes more and more common in all groups of schistosome larvae the fundamental importance of the glands in the economy of the cercaria as an invading organism, becomes established.

In studying immature cercariae of *S. japonicum* in which the caudal portion was just beginning to be differentiated from the body proper, these cephalic glands, all of one type, have been observed. This observation accords with that of Faust (1920, Fig. 6) in which the cephalic glands of the cercaria of *S. mansoni* were found already formed and differentiated at a similarly early stag of development of the larva.

The hollow piercing spinose tubes which cap the duct openings of the cephalic glands have been generally observed in mammalian schistosome cercariae since they were first described in non-mammalian forms (Faust, 1919: 167–168). Their function is probably specific, namely, to drill microscopic holes in the skin of the definitive host at the time of invasion, so that the proteolytic secretions of the cephalic glands may the more readily digest away the host tissue. In the schistosome cercariae this function is an established fact. Even non-mammalian cercariae, when placed on the back of the hand of one of us (E. C. F.) and allowed to attack for a half hour, produced an itching sensation and caused a demonstrable exanthem. Moreover, *schistosome dermatitis,* at the time of invasion of the cercaria of *S. japonicum,* is regarded by some investigators as a clinical sign as definite as "ground itch," and while it is probably caused by the combined mechanical and digestive action of the cephalic glands and their products, it is an important factor in the invasion. The miracidium is able to enter the soft tissues of the snail without armature or mechanical batteries, but the more resistant skin of the mammalian host undoubtedly requires a more effective assault.

The head gland is a single median organ lying within the oral sucker complex (Fig. 21). The content is much more homogeneous than that of the cephalic glands and the staining reaction in the mature larva is slightly basophilic. Moreover, the gland develops much later than the cephalic glands and degenerates immediately on

the invasion of the definite host. It seems improbable that it can be of any considerable assistance to the cercaria during the stage of invasion.

The genital anlage.

Although the sexes are separate in the adult *Schistosoma japonicum*, and although this sexual difference has been demonstrated relatively early in the young worms after they have reached the portal vein of the definitive host (Cort, 1921), the genital *anlage* is extremely simple in the cercaria. It consists of a single oval cluster of small cells with granular contents, situated directly behind the ventral sucker, and usually somewhat smaller in diameter than this organ. We have been unable to observe in different specimens any differences in size, shape or position of this *anlage* which might be interpreted as distinguishing male and female larvae. Furthermore, the difficulties in making accurate measurements of either living or preserved specimens offer an obstacle to any attempt to differentiate the cercariae on a size basis, such as Cort suggests from his studies on an eye-spotted non-mammalian schistosome (1921: 7–9). In spite of this lack of positive data of sex dimorphism at the cercaria stage, all of the experimental work points to the sexual difference in the cercariae which show no outward signs of dimorphism.

Our own data confirm those of Japanese workers on the problem, that in most cases, where cercariae from a single snail are used to infect a mammalian host, only one sex is found in the infection. It seems highly probable, therefore, that cercariae from a single brood are usually a single sex. A more detailed consideration of this problem will be taken up in a later section of this paper.

The cercaria as an invading organism.

In one respect the method of infecting the definitive host, utilized by the schistosome cercaria, is unique among trematode larvae. This fluke does not make use of a secondary intermediate host, either as incubator or mechanical transfer agent. Nor does it encyst on or within some article of food of the definitive host. Its method of invasion is a direct penetration of the exposed skin (and possibly oral mucosa).

In the laboratory cercariae of *S. japonicum* may be obtained in several ways. If infected snails harboring mature cercariae, which have been in a state of apparent desiccation for some days, are placed in water, they become active almost immediately and soon discharge cercariae singly or in groups, depending on the amount of infection in

the snail. The period of greatest discharge extends over three or four hours, soon after the immersion of the snail in the water, although more prolonged discharge may take place over a longer period. After a period of such discharge there is an interval of at least several hours, before any considerable second discharge takes place. If these snails are placed in a dry state and allowed to "rest" for a week or ten days they will usually yield additional mature larvae. We have discovered that infected snails, which were thought to have discharged their entire number of mature cercariae, contained, on dissection, large numbers of mature and maturing larvae, which would have been discharged no doubt at a later period. Such snails yield viable cercariae, although the larvae are not as numerous as the ones which erupt in showers after a resting period.

The condition of viability or ability to infect the definitive host extends over a relatively wide range of mature and maturing larvae. On the one hand, larvae which have been artificially teased out of sporocysts and have not yet taken up a free-living existence, and which from the point of view of motility might possibly be considered slightly immature, have been found experimentally to produce normal infections, while, on the other hand, larvae which have been free in the water for thirty hours or more are also known to be infective. Nevertheless, our heaviest infections have been secured from those cercariae which erupted freely from the snails soon after the snails were first placed in water. Immersion of a dog in such "infected water" for an hour produced in one instance an infection which resulted in obtaining at autopsy 14 days later 39,096 living worms.

The cercaria swims rapidly during its active period, but the greatest part of the free-living period is consumed as a quiescent or squirming organism in the surface film or (in the laboratory) attached to the side of the container. Worms that have become decaudated are still able to move on the surface without difficulty and must not be confused with the post-infective organisms. Our observations lead us to believe that more infection takes place through contact of the mammal with the surface film of "infected water," than through a chemotactic response of the cercaria to the mammal when the cercaria is several times the body distance from it. In this respect it differs markedly from the miracidium. When once a direct or near contact is established with the skin of the mammalian host the cercaria takes hold actively and drills its way into the skin. As in other related cercarial forms, this consists of a hammering movement, similar to that of a compressed air drill, while the organism has, in addition to the mechanical hollow boring

spines, the proteolytic action of the cephalic gland juices which are actively poured out during this period. We have not determined the minimum period required for "infected water" in contact with the skin of a suitable host to produce an infection in the host. However, an hour's partial immersion in such an infected medium has been found adequate to infect experimental animals, even when they were dried off immediately after immersion to prevent chilling. It is altogether likely that a mouse becomes infected much more readily than a mammal with a thicker skin. The thick skin of the water buffalo may explain the apparent immunity of this animal which wades in infected areas in China without any clinical evidence of the disease.

The post-infective stage of the cercaria.

The post-infective cercaria is senescent. This period arrives in from thirty to seventy-two hours after eruption of the cercaria from the snail, depending on the virility of the organism at the time of eruption. It arrives much earlier in specimens artificially teased out of the liver tissue of the snail. It consists in the discontinuance of locomotion on the part of the cercaria and a shortening of the body parts, particularly the curling up of the tail furci and the contraction of the caudal trunk. The oral sucker then becomes partly inverted. This is an entirely different state from that of the contracted viable organism at the surface film. In the senescent cercaria which has reached this stage cytolysis soon results and the organism succumbs.

D. The development of *Schistosoma japonicum* within its definitive host.

Much has been written about the route of invasion of *Schistosoma japonicum* within the mammalian host, but remarkably little has been discovered about the development of the blood-fluke itself within its final host. In fact, only one investigator, Cort (1921), has undertaken to study and correlate the stages of development of this fluke from the viewpoint of the worm. His data constitute a valuable contribution to the morphology and ontogeny not only of this particular blood-fluke, but of all mammalian schistosomes.

Material.

We have had the opportunity of studying all the developmental stages of the young schistosome in experimental animals. For this study viable cercariae of *Schistosoma japonicum* from Chinese and Japanese molluscs were used to infect laboratory animals. For the

earlier stages mice and rabbits were utilized. These were supplemented in the later stages of the schistosomula by dogs. The animal to be infected was placed for one hour in water in which a large number of viable cercariae was known to be present. Some of the later stages were obtained from dogs which had been infected by subcutaneous injection of cercariae. In view of the fact that all of this work was done in Peking, where the disease does not occur, on animals locally bred, natural infections with the worm could not have taken place, and, therefore, need not enter into this discussion.

Method of examination.

Our material was all obtained and was studied, while yet alive. The hosts were autopsied and the organs and tissues were washed, irrigated and dissected in citrate saline solution. Advantage was taken of the fact that the worms sink to the bottom of the container more rapidly than do the red corpuscles, so that by successive washings and decantations, a residue of clear fluid was finally obtained, in the sediment of which the worms, if they had been present in the organ or tissue examined, were detected under the low power of the binocular dissecting microscope. They were then transferred to watch glasses or glass-slides and studied under the compound microscope. Observations and measurements were made on the living worms, after which the worms were killed in 10 per cent. formalin and comparative observations made.

The stages of development.

(Figs. 22 to 33; Photomicrographs 29 to 42.)

Fujinami and Nakamura (1909), Fujinami (1911), Miyagawa (1913, 1916) and others have all obtained young stages of the schistosomula from the body of the definitive host and have figured them in their published data, but in no instance have they described them in sufficient detail to constitute a basis for recognition or classification of stages. Cort (1921: 6) records having obtained three young worms from an infected laboratory mouse, autopsied forty hours after infection, but does not describe them. His earliest stages, on which he based his classification of the developing worms, were obtained from mice examined on the tenth day after exposure. Cort's youngest stage [Pl. I, 1 (F. or M.)] corresponds to our sixth stage and is, therefore, considerably advanced over the earliest stages which we have obtained. In all, we have been able to recognize twenty-four stages of development of the blood-fluke in the mammalian host. Because these

are relatively constant and can be recognized without great difficulty either from size ratios or from internal structures, we propose that Greek letters from α to ω inclusive be used to designate these stages. We accept Cort's stages 1 (F. or M.), and 2 (M) to 18 (M) and refer them stage for stage to our series, in which they constitute stages ζ and η to ψ inclusive. Stage ω (♂) represents a size, and perhaps a maturity phase, more advanced than any figured by Cort. We also accept his stages 2 (F.) to 9 (F.) and refer them stage for stage to our series, in which they constitute stages η to ξ. Between Cort's stage 9 (F.) and 10 (F.) we have found it necessary to interpolate our stage o, and between his stages 10 (F.) and 11 (F.) we have been obliged to interpolate our stages ρ and σ. His stages 11 (F.) and 14 (M.) correspond to our stage τ. This differentiation is made partly on the basis of mean average length and on the maturity of internal structures.

When the cercaria of *Schistosoma japonicum* penetrates the skin of the mammalian host it is deprived of its tail. In fact, decaudation frequently occurs in normal viable cercariae in water not in contact with a mammal. *The worm at this period ceases to be a cercaria and becomes an agamodistome.* Except for the absence of a tail, it possesses on entering the final host a full complement of organs of the free-swimming cercarial stage. The cephalic glands with their crowned caps, together with the head gland, are the batteries of offense, by which the larva gains entry through the skin. It seems likely that this migration through the several layers of skin occupies some time, since we have been unable to obtain the worms in the lymph nodes or lungs before the second day.

The earliest stage (α, Fig. 22; Photomicrograph 30), obtained by us, was dissected from the inguinal lymph nodes of a mouse fifty-one and one half hours after exposure, and from the popliteal lymph nodes of a rabbit twenty three hours after exposure. By comparison with the decaudated cercaria certain structures are seen to have remained unchanged, while other organs have become fundamentally modified. When the tail of the cercaria was left behind, the second flame-cell of the posterior group in the excretory system was also pinched off with it, leaving an open capillary with a pore opening through the posterior integument of the worm. This condition prevails in the α stage of the schistosomulum, the tube still opening to the outside (Fig. 22). The cephalic glands are easily recognized and the spine-capped openings are prominent, although the contents of the glands have changed. The glands are shrunken, as are also the ducts, which frequently are devoid of contents. The head gland has not been observed at this

stage or later. More noticeable is the modification of the gut. Its inner end has become enlarged and shows definite indications of lateral ceca. Anterior to this position it is slightly enlarged. Moreover, it contains granules of material that have apparently come in through the oral opening. No red blood corpuscle inclusions have been observed. Furthermore, the gut is slightly longer than in the cercaria stage, although it still reaches only about half-way down to the ventral sucker.

The external appearance of the worm is practically identical with that of the organism at the time of invasion. It is spinose. The body averages from 100 to 120 μ in length, and measures about 29 μ in width. The oral sucker is noticeably larger than the acetabulum. The relation of gut opening and cephalic gland duct openings has become somewhat modified in that the former has advanced anteriad, while the latter have come to be set out on a dorsal labium (*dl*), above the former.

The β stage (Fig. 23; Photomicrograph 31) has been obtained readily from irrigations and dissection of lungs of mice and rabbits from the second to the fourth day following infection, and from the popliteal lymph nodes of the rabbit, on the second and third days following infection. It represents a definite advance over the α stage in all critical points. It is larger, measuring from 120 to 180 μ in length by 29 to 37 μ in width, at the ventral sucker. The excretory system has become balanced by a compensatory division of the anterior flame-cell of the posterior group, so that there are now again two pairs of flame-cells for each side of the body, but with this difference from the cercarial stage, that all of these flame-cells are now within the body proper. The cephalic glands are present, but their contents have been all used up. The spinose duct openings are still prominent. The gut has become enlarged and elongate and the ceca contain red blood corpuscles. The mouth has come to assume a central position in the oral sucker.

The γ stage (Fig. 24; Photomicrograph 32) is typically found in the liver on the third or succeeding days after infection, although it occurs in the lungs, lymph nodes, and even the pleural cavity. It has increased in size, so that it measures from 160 to 200 μ in length by 23 to 40 μ in width, at the ventral sucker. The dorsal labium (*dl*), with the spinose duct opening, is conspicuous. The cephalic glands and their ducts have become vestigial, although they can be recognized. The first dichotomous division of the excretory capillaries and flame-cells usually occurs at this stage, so that two quartet groups of flame-

cells result for each side of the body. The gut has become enlarged, and, in live specimens, apparently functional, for it not only contains red-blood cells, but also the dark brown pigmentation so characteristic of the older specimens. The gut has not yet reached the acetabulum.

With the δ stage (Fig. 25; Photomicrograph 33) increase in size continues. The specimens measure 140 to 260 μ in length by 26 to 60 μ in width. This stage has been found in the lungs, in irrigations through the capillaries of the leg and through the mesenteric vessels, as well as in the liver. The dorsal labium is still present, but the cephalic gland ducts and spinose caps have all disappeared. The animal has by this time reached its destination or is in direct line for transfer passively through the blood to the portal system. Otherwise it is tissue locked, for it does not have the equipment for penetrating solid tissues. At this period the ceca of the gut have become elongate and have reached the acetabulum. In live specimens the gut is entirely filled with red cells and pigment granules.

The ϵ stage (Fig. 26) shows both external and internal growth and differentiation. Specimens of this stage measure from 170 to 280 μ in length by 25 to 70 μ in width. The dorsal labium which had been a prominent structure in the preceding stages has entirely disappeared. From this time on the oral sucker functions in the ingestion of food. Just behind the oral sucker the esophageal glands (*eg*) become developed and probably assist in the digestion of food. The esophagus extends nearly to the acetabulum and the ceca bow out around and behind that organ. Meanwhile another bifurcation of the flame-cells and capillaries has occurred, so that each original basic unit of the system now contains eight elements. No differentiation of sexual structures internally has been observed up to and including this stage. At this period in development the worm might be easily mistaken for the decaudated cercarial stage of many groups of flukes.

The considerable increase in length coupled with a decrease in width from the β to the ϵ stages is explained in part on the basis of a greater observed extensibility of the worm. This is probably related to its passage through capillaries of the blood.

Beginning with the ζ stage, and inclusive through adolescent and adult forms, the growth and differentiation has been described in detail by Cort (1921). Cort has described the early differentiation of sex (his stage 2, our η stage) and the differences of size relations of the male and female from this period on. Histogenetic differentiation of the genital *anlage* takes place late and cannot be made out until the worms are readily distinguishable with the naked eye. Actual develop-

TABLE IV.

Stages in the development of young and maturing Schistosoma japonicum in mice.

Designation of stage.	α	β	γ	ϑ	ε	ζ	η	θ	ι	κ	λ	μ	ν	ξ	ο	π	ρ	ϱ	τ	υ	φ	χ	ψ	ω
Cort's corresponding series.						1 ♀ + ♂	2 ♀ + ♂	3 ♀ + ♂	4 ♀ + ♂	5 ♀ + ♂	6 ♀ + ♂	7 ♀ + ♂	8 ♀ + ♂	9 ♀ + ♂	10 ♂	10 ♀ 11 ♂	12 ♂	13 ♂	11 ♀ 14 ♂	15 ♂	16 ♂	17 ♂	18 ♂	
Inclusive measurements (in microns and millimeters) of length and breadth.																								
	100–120 x 29 μ.	120–180 x 29–37 μ.	160–200 x 23–40 μ.	140–260 x 26–60 μ.	170–280 x 20–70 μ.	♀	200–290 x 25–35 μ.	250–280 x 75–90 μ.	420–500 x 90–100 μ.	500–600 x 90–130 μ.	600–800 x 100–140 μ.	.9–1.5 x 70–150 μ.	1.0–1.2 x 100–130 μ.	1.4–1.8 x 100–120 μ.	2.0–2.5 x 100–120 μ.	2.0–3.6 x 90–150 μ.	3.9–5.0 x 90–130 μ.	6.0–6.6 x 100–130 μ.	7.0–7.6 x 130–200 μ.	8.0–8.4 x 100–110 μ.	8.3–9.0 x 100–110 μ.	9.2–9.8 x 100–110 μ.	10.0–10.8 x 100–110 μ.	11.0–11.9 x 100–110 μ.	12.0–12.8 x 100–110 μ.
						♂	200–220 x 29–44 μ.	230–280 x 120–130 μ.	360–480 x 100–150 μ.	390–530 x 120–150 μ.	480–690 x 135–160 μ.	600–800 x 120–180 μ.	700–900 x 120–210 μ.	870–1500 x 150–210 μ.	1.38–1.70 x 180–225 μ.	1.6–1.8 x 160–260 μ.	1.6–2.0 x 130–280 μ.	2.0–2.3 x 180–260 μ.	2.3–2.6 x 200–280 μ.	2.5–2.8 x 200–300 μ.	3.0 x 260–300 μ.	5.3–6.0 x 300–350 μ.	6.0–6.6 x 300–400 μ.	7.0–10.0 x 400–1000 μ	10.0–12.0 x 800–1200 μ
Infective period and location in host.																								
1. 51½ hours.																								
a. Inguinal lymph gland	10																							
b. Pulmonary irrigation and dissection		13																						
2. 70 hours.																								
a. Inguinal lymph gland	4	6																						
b. Pulmonary irrigation and dissection		60	15																					
d. Liver irrigation and dissection			1																					

TABLE IV.—*Continued.*

| | | |

TABLE IV.—*Continued.*

Designation of stage.	α	β	γ	ϑ	ε		ζ	η	θ	ι	κ	λ	μ	ν	ξ	ο	π	ρ	σ	τ	υ	φ	χ	ψ	ω
Cort's corresponding series.							1 ♀ + ♂	2 ♀ + ♂	3 ♀ + ♂	4 ♀ + ♂	5 ♀ + ♂	6 ♀ + ♂	7 ♀ + ♂	8 ♀ + ♂	9 ♀ + ♂	10 ♂	10 ♀ 11 ♂	12 ♂	13 ♂	11 ♀ 14 ♂	15 ♂	16 ♂	17 ♂	18 ♂	
Inclusive measurements (in microns and millimeters) of length and breadth.																									
	100–120 x 29 μ.	120–180 x 29–37 μ.	160–200 x 23–40 μ.	140–260 x 26–60 μ.	170–280 x 20–70 μ.	♀	200–290 x 25–35 μ.	250–280 x 75–90 μ.	420–500 x 90–100 μ.	500–600 x 90–130 μ.	600–800 x 100–140 μ.	.9–1.5 x 70–150 μ.	1.0–1.2 x 100–130 μ.	1.4–1.8 x 100–120 μ.	2.0–2.5 x 100–120 μ.	2.0–3.6 x 90–150 μ.	3.9–5.0 x 90–130 μ.	6.0–6.6 x 100–130 μ.	7.0–7.6 x 130–200 μ.	8.0–8.4 x 100–110 μ.	8.3–9.0 x 100–110 μ.	9.2–9.8 x 100–110 μ.	10.0–10.8 x 100–110 μ.	11.0–11.9 x 100–110 μ.	12.0–12.8 x 100–110 μ.
						♂	200–220 x 29–44 μ.	230–280 x 120–130 μ.	360–480 x 100–150 μ.	390–530 x 120–150 μ.	480–690 x 135–160 μ.	600–800 x 120–180 μ.	700–900 x 120–210 μ.	870–1500 x 150–210 μ.	1.38–1.70 x 180–225 μ.	1.6–1.8 x 160–260 μ.	1.6–2.0 x 130–280 μ.	2.0–2.3 x 180–260 μ.	2.3–2.6 x 200–280 μ.	2.5–2.8 x 200–300 μ.	3.0 x 260–300 μ.	5.3–6.0 x 300–350 μ.	6.0–6.6 x 300–400 μ.	7.0–10.0 x 400–1000 μ.	10.0–12.0 x 800–1200 μ.
Infective period and location in host.																									
5. 144 hours.																									
Series *A*.																									
b. Lung irrigation and dissection			5	12	13																				
c. Pleural washings		4	4																						
d. Liver irrigation and dissection				24	63		47																		
Series *B*.																									
d. Liver irrigation and dissection		3	5	5	4																				
6. 168 hours. (7 days)																									
b. Lung irrigation and dissection				1	1																				

TABLE IV.—*Continued.*

168 hrs. (*cont'd*)																															
c. Pleural washings					1		1																								
d. Liver irrigation and dissection	♀				4		3	2	1																						
	♂				3		6	6	3																						
	☿		4	7	4																										
7. 192 hours. (8 days)																															
Series *A*.																															
b. Lung irrigation and dissection				1	2		1																								
c. Pleural washings				2																											
d. Liver irrigation and dissection	♀				3		1																								
	♂				2		1		2																						
	☿							5	12	1																					
Series *B*.																															
b. Lungs			1	1	1																										
c. Pleural			2	1																											
d. Liver.	♀				11		5	2																							
	♂				7		15	13	3	1	2																				
	☿			5																											
8. 216 hrs. (9 days)																															
Series *A*.																															
b. Lungs.				1																											
d. Liver.	♀				2		3	4	3	5	2																				
	♂				9		13	18	13	5	3																				
	☿			9																											

TABLE IV.—*Continued.*

| Designation of stage. | Cort's corresponding series. | Inclusive measurements (in microns and millimeters) of length and breadth. | | |

TABLE IV.—*Continued.*

10. 264 hours. (11 days)																											
d. Liver and ♀					1		2	2	8	4	3																
e. mesenteric ♂					1		5	5	12	14	14	9	4	1	1												
veins. ☿				1(?)																							
11. (12 days)																											
d. Liver and ♀							4	8	12	20	11	1	1														
e. mesenteric																											
veins. ♂							3	5	11	18	24	9	8	2	1	1											
12. (13 days)																											
d. Liver ♀							4	4	7	10	9	7	3	2	1												
♂							3	4	6	13	12	7	5	3	3	1	1										
13. (14 days)																											
d. Liver ♀								3	2				1	1													
♂								3	3	7	8	8	7	8	4	2		1									
14. (17 days)																											
d. Liver ♀									2	5	4	9	10	6	2												
♂										2	4	9	7	2	2	2	6	4	3								
15. (19 days)																											
d. Liver. ♂ (only)										1	1	2	4	6	6	5	6	4	3	2							
16. (31 days)																											
d. Liver ♀													1	2	5	4	4	4	2								
♂												1(?)									1	6	1				

TABLE IV.—*Continued.*

Designation of stage.	α	β	γ	ϑ	ε	ζ	η	θ	ι	κ	λ	μ	ν	ξ	ο	π	ρ	σ	τ	υ	φ	χ	ψ	ω
Cort's corresponding series.						1 ♀ + ♂	2 ♀ + ♂	3 ♀ + ♂	4 ♀ + ♂	5 ♀ + ♂	6 ♀ + ♂	7 ♀ + ♂	8 ♀ + ♂	9 ♀ + ♂	10 ♂	10 ♀ 11 ♂	12 ♂	13 ♂	11 ♀ 14 ♂	15 ♂	16 ♂	17 ♂	18 ♂	

Inclusive measurements (in microns and millimeters) of length and breadth.

	100–120 x 29 μ.	120–180 x 29–37 μ	160–200 x 23–40 μ.	140–260 x 26–60 μ.	170–280 x 20–70 μ.	♂ 200–220 x 29–44 μ.	♀ 200–290 x 25–35 μ.	230–280 x 120–130 μ.	250–280 x 75–90 μ.	360–480 x 100–150 μ.	420–500 x 90–100 μ.	390–530 x 120–150 μ.	500–600 x 90–130 μ.	480–690 x 135–160 μ.	600–800 x 100–140 μ.	600–800 x .9–1.5 x 120–180 μ.	70–150 μ.	700–900 x 120–210 μ.	1.0–1.2 x 100–130 μ.	870–1500 x 150–210 μ.	1.4–1.8 x 100–120 μ.	1.38–1.70 x 180–225 μ.	2.0–2.5 x 100–120 μ.	1.6–1.8 x 160–260 μ.	2.0–3.6 x 90–150 μ.	1.6–2.0 x 130–280 μ.	3.9–5.0 x 90–130 μ.	2.0–2.3 x 180–260 μ.	6.0–6.6 x 100–130 μ.	2.3–2.6 x 200–280 μ.	7.0–7.6 x 130–200 μ.	2.5–2.8 x 200–300 μ.	8.0–8.4 x 100–110 μ.	3.0 x 260–300 μ.	8.3–9.0 x 100–110 μ.	5.3–6.0 x 300–350 μ.	9.2–9.8 x 100–110 μ.	6.0–6.6 x 300–400 μ.	10.0–10.8 x 100–110 μ.	7.0–10.0 x 400–1000 μ.	11.0–11.9 x 100–110 μ.	10.0–12.0 x 800–1200 μ.	12.0–12.8 x 100–110 μ.
Infective period and location in host.																								
17. (41 days)																								
d. Liver ♀														1	1	2								
d. Liver ♂																	2	3	1	2	2	2	3	1
18. (56 days)																								
d. Liver. ♂ (only)																		1	2	3	6	3	1	
19. (78 days)																								
d. Liver. ♂ (only)																					2	5	8	

ment of sexual organs does not take place until the worms are well along toward adult size. In all of these details our observations confirm Cort's. In the early days of infection (6 to 10 days), however, we have usually been able to differentiate sex in the ϵ and ζ stages and to separate them from the earlier worms of our undifferentiated series. In some instances, there were also ϵ and ζ stages which had yet remained undifferentiated. Our data lead us to believe that the critical period, when differentiation can first be detected, lies between the ϵ and ζ stages. This can be most readily observed in liver irrigations, where in heavy infections 100 or more worms occur during the sixth to tenth day after infection.

There is sufficient evidence to conclude that the normal development of the worm takes place only in the hepatic portal system. Only the earlier stages are found in the organs and tissues through which the worm migrates into the portal system. After five days the worms are no longer found in the peripheral lymph nodes, and even on the fifth day those found in lymph nodes show degenerative changes. They never develop beyond the γ stage in these foci. They occur in the lungs from the second to the tenth day after infection, after which they can no longer be recovered from the lungs. This series shows some growth over the lymph node series, for it includes stages β to ϵ. This seems to indicate that a certain amount of growth can take place in the lungs, but this development is limited. In mice we have been able to recover worms from the pleural cavity from the fourth to the eighth day after infection. However, the stages of development in this locality are few, including only the β, γ and δ forms. On the eighth day all of the specimens found in the pleural cavity are degenerate. From these data we may conclude that (1) normally α and β stages occur in the peripheral lymph nodes and that, to be successful, migration out of these localities into the blood system must take place before the fifth day; (2) that β, γ, δ, stages normally occur at the time the worms pass through the lungs and that the worms must have emigrated from this locality before the eleventh day after infection, in order to reach the liver; and (3) that although stages β, γ and δ have been recovered from the pleural cavity (in mice), the period of existence in this locality is short (only from the fourth to the eighth day), and the means of securing nourishment are scant.

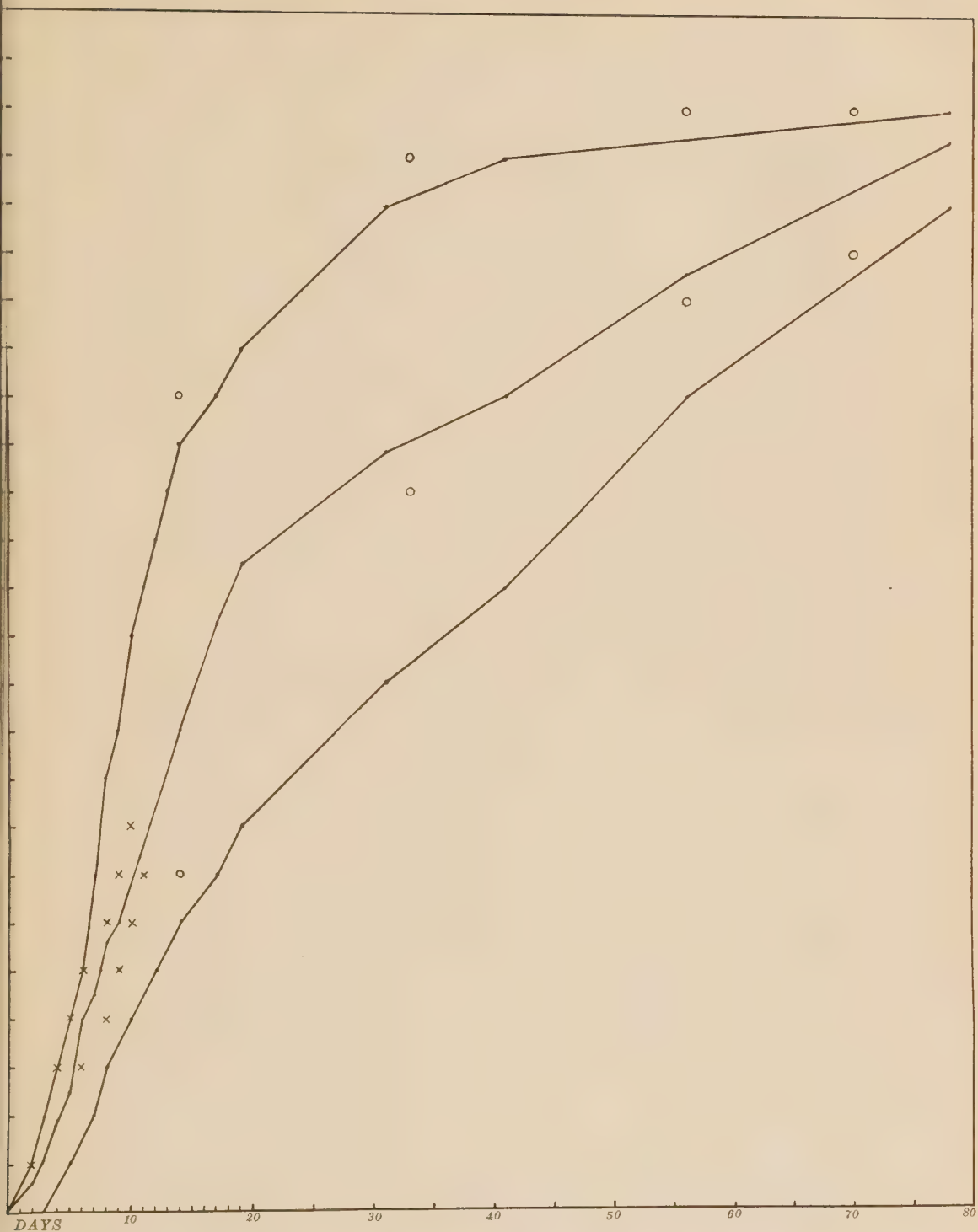
When the worms once reach the portal system development is rapid. The β stage is the youngest recovered, while the γ stage is probably the first one usually to arrive. These stages have been secured on and after the third day following infection (Table IV), and have been

found through the fifth day. After that the youngest stages in the series become steadily older and more differentiated. The δ stage was last found on the eleventh day following infection, but the specimens of this stage, on both the tenth and eleventh days, were degenerate. By the fourteenth day the η stage is the youngest. On the seventeenth day the ϑ stage is the youngest, and on the nineteenth day the λ stage is the least mature. This same stage is the youngest found in 31 day infections in which a large percentage of the worms are sexually mature. We have observed few degenerate early stages in the liver. We believe, therefore, that the larval stages α to δ are typically migration types; that the worm normally reaches the hepatic portal system before this period is passed; that, failing in this, its means of penetration, the cephalic gland secretion, disappears and it degenerates *en route*. Furthermore, once the liver is reached, the young larva rapidly develops to the adolescent stage, and usually to maturity.

Curve of growth of the maturing Schistosoma japonicum.

Our material from experimentally infected mice has made it possible for us to study the successive daily changes of the worm from the second through the fourteenth day after infection and, after that day, all the critical stages through to the seventy-eighth day following infection. Moreover, certain stages from rabbits and dogs have contributed comparative data. From these data we have been able to construct a *Curve of Growth* (Textfigs. *C*, *D*) for the schistosome during this period, which makes the interpretation of the developmental period much simpler. The curve, as expressed in stages of growth, is shown in Textfigure *C*. The days following infection are indicated on the horizontal axis and the growth in stages on the vertical axis. For mice the curve shows three values: (1) the maximum growth stage, (2) the minimum growth stage, and (3) the mean average growth. The points of maximum and minimum growth for rabbits and dogs are indicated respectively by an "X" and an "O," and, although not entirely coincident with the other series, indicate very little variation due to differences of host.

During the first six days after infection the migration into the seat of residence in the portal system and the accommodation of the worm to the new residence requires practically all of the energy of the worm. In spite of this requirement, at the end of six days the spread of the curve covers five stages as compared with two stages at the end of the second day. Furthermore, the mean average lies near the maximum, having reached the ϵ stage. From this period on to the end of the



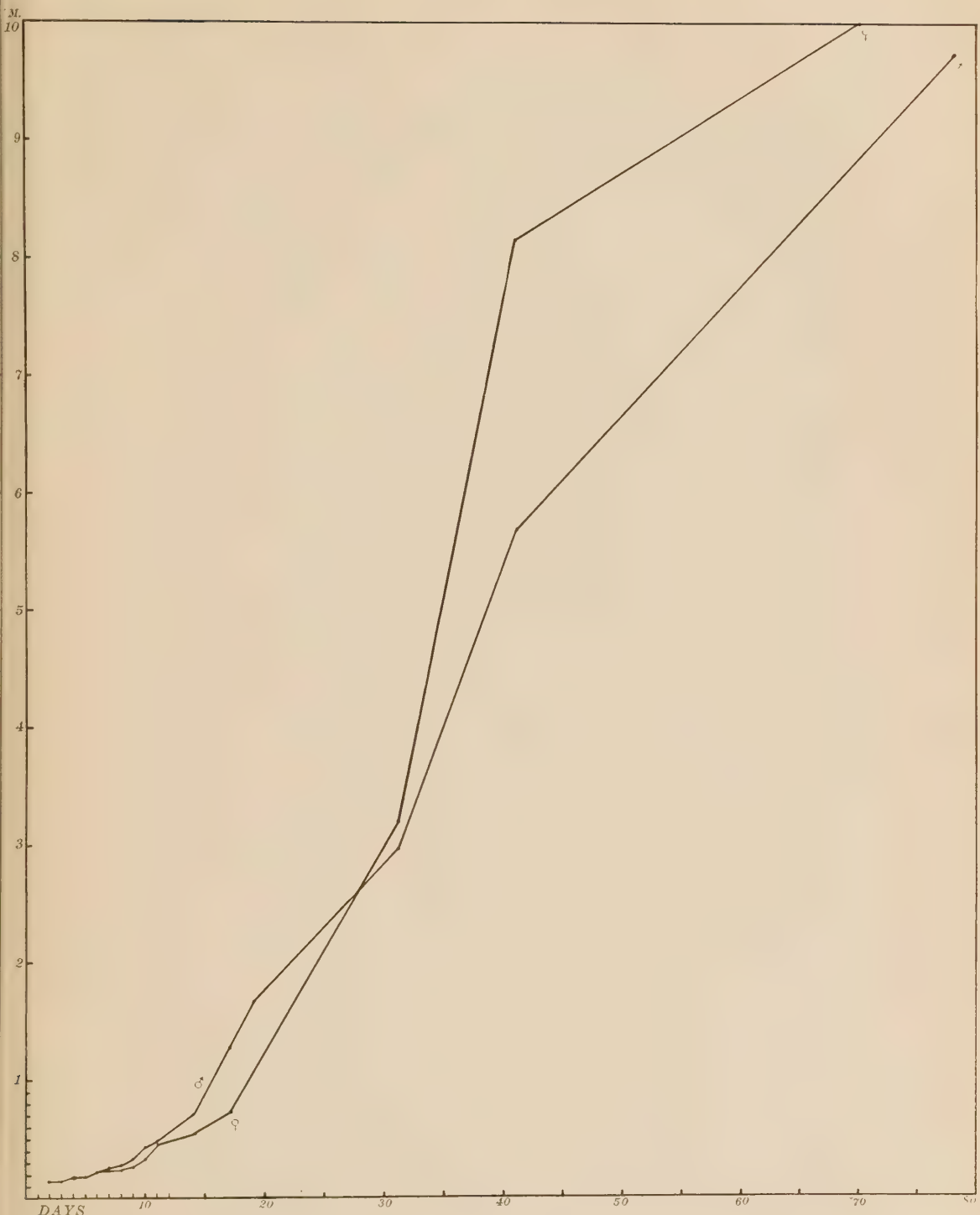
TEXTFIG. *C*. Curve of growth of *Schistosoma japonicum* within the definitive host, based on stages of maturity.

twelfth day rapid growth takes place, sometimes at the average maximum rate of two stages a day. At the end of this period the spread of the curve covers ten stages, while the mean is five stages behind the maximum.

Between the eighth and the tenth days there occurs the greatest percentage growth in the worm. From the tenth to the seventeenth days a gradual increase in the spread of the curve occurs, although the maximum and mean averages are somewhat slower in rising than in the preceding period. From that time on growth is gradually retarded. This is probably linked up with the high degree of internal differentiation which must take place at this time. Not only is the average growth less per day, but the spread of the curve now becomes less. This is particularly apparent after the nineteenth day. By the fortieth day the maximum of the curve has practically reached its upper limit, and progresses thereafter very slowly. In the mouse this is usually the most advanced stage found. The mean average still lies five stages behind the maximum for this day, while on the seventy-eighth day the mean lies only one stage behind the maximum, and the spread of the curve covers only three stages.

Since our measurements and observations indicate that certain worms are still so young on the twelfth day that their sex cannot be determined, it seems necessary to regard them as late arrivals in the portal system. This delay in arrival may amount to nine or ten days, reckoning the third day after infection as the first one on which worms were first found in the portal system. It is necessary, therefore, to keep this fact in mind when referring to the minimum growth of any series after the third day. However, the growth differences of any series cannot be all accounted for by this fact and must be considered, in part, as due to individual variations.

The above curve has been based on the maturity growth of the schistosome over a given period of time. It includes both males and females, as well as healthy undifferentiated worms, and takes into consideration after the fifth day only those individuals found in the portal system. This presupposes that the stages of growth have been carefully tested for both males and females and correlated. As a test for the system which Cort proposed (1921), and which we have adopted, we plotted separate curves for males and females, beginning on the sixth day and continuing through to the forty-first day, basing the curve not on stages of maturity, but on actual growth in length (Textfig. *D*). Previous to the sexual differentiation, growth in length had taken place extremely slowly, but from that time on (the sixth day) through the twenty-seventh day the size growth was considerable.



Textfig. *D*. Curve of length-growth of the male and female *Schistosoma japonicum* in mice.

During this period the males grew more rapidly than the females, but following this period (28th to 41st days) the females made tremendous increases, so that they left the males far behind. This can be tested out anywhere along this part of the curve by measuring a series of specimens of both sexes from the same batch and computing the mean average for the series. The spread of the two curves is also important. On the sixth day the range extended from 165 to 300 μ. On the fourteenth the male series extended from 250 μ to 2.3 mm., and the female series from 250 μ to 1.8 mm. By the thirty-first day the spread of the female curve was wider than that of the male (♀ from 1 mm. to 7.6 mm.; ♂ from 0.8 mm. to 6.6 mm.). Following this the extremes of the male series approach one another gradually, while the extremes of the female series approach one another rapidly. At the end of forty-one days the longest and shortest females measure 9.8 mm. and 8.0 mm., while the corresponding figures for the male are 10.0 mm. and 1.38 mm. This points to a single conclusion, namely, that the females not only grow much more rapidly in length after the twenty-seventh day, but also mature much more rapidly than the males.

A comparison of the two types of curve (Textfigs. *C*, *D*) shows that the maturity growth curve is not appreciably affected up to the thirty-first day by any differences in growth between males and females of the same series. After that time, however, the average of the series is definitely raised by the rapid maturing of the females. At the end of two to three months, after infection, the mean averages of the male and female series again approximate one another.

Other factors which might seriously affect the growth and maturity rate of the worms, once they have arrived within the portal system, are the size of the host, the number of worms that have arrived within the portal vessels, and the maturity stimulus produced by one sex upon the other.

As a test of the effect of the host upon the size development of the worms we have measured and examined worms of similar series from rabbits and dogs, and have compared them with our more elaborate series from mice (see Textfig. *C*). Our examinations indicate that the series in the rabbits falls within the minimum-maximum spread of the mouse series, although the mean average of development is slightly higher. The series in the dog, however, has a slightly more mature aspect as early as the fourteenth day, and continues this trend over the mouse series through to complete maturity. At the end of the growth and maturity period, however, both mouse and dog series show the same mean averages of growth in size and maturity and the same

curve spread. This seems to indicate, therefore, that the size of the host animal is significant during the period of rapid development, although the end results are the same. In other words, the same type of curve expresses the growth of the worm in these several hosts, although the upper limits of the curve are reached more rapidly in the series in moderately large animals.

In extremely heavy infections the worms seldom reach maturity. This is caused, first of al , not by the inability of the worms to mature, but by their pathogenic effect on the host, causing death while the worms are still at a period in their development when maturity is not to be expected. For this reason it is difficult to infect mice heavily and keep them alive a sufficient length of time to allow the worms to mature. In extremely heavy infections in dogs the same condition occurs. It is conceivable, likewise, that in endemic centers of infection, human beings may become so heavily infected that the worms may cause death long before their maturity and, therefore, before the eggs could be found in the feces, even if medical examination were available. However, it has been our observation that in several instances as many as several hundred male and female worms lived to maturity in an experimental dog, while several worms (up to twenty or thirty) may mature in a mouse. In two puppies of one series in which both were heavily infected, one dog died on the fourteenth day from the result of an overwhelming infection. At autopsy nearly 40,000 worms were recovered from the portal system. The other dog lived to the thirty-third day, when he succumbed to the infection. On the twenty-ninth day eggs first appeared in the feces and on the thirtieth day mature miracidia were hatched from ova. At autopsy more than 10,000 mature and maturing worms were recovered. It is, therefore, possible for some individuals with an overwhelming infection to live to maturity and permit of laboratory diagnosis through the presence of eggs in the feces. During maturity the pathogenic effect on the host is a more serious factor. This problem will be discussed later in our study.

The ability of the host to accommodate itself to the presence of a considerable number of foreign organisms in its portal system deserves consideration.

It seems probable that the worms, on arriving in the portal system, first congregate in the liver and remain there for some days until they have partly or nearly matured. This is borne out by our studies in which the intra-hepatic infection during this growth period was much heavier than that of any other part of the portal system or mesenteric

system. As maturity comes on these worms are found in increasing numbers in the extra-hepatic portion of the system, so that experimental animals harboring mature worms, if autopsied before death, have by far the largest numbers in the mesenteric veins. As this extra-hepatic invasion proceeds, the vessels accommodate themselves more and more to the parasites by distention, so that the worm may be found in the smallest venules of the intestines and even, at times, in the capillaries. In light infections probably only the mesenteric veins are invaded, but in heavy infections rectal, splenic and gastric vessels are also utilized as an overflow to the more centrally located vessels.

In a few instances we have been puzzled in interpreting specimens of *Schistosoma japonicum* obtained from experimental animals (Photomicrograph 41). One mouse, infected with material from a Japanese source, lived for several months without showing any symptoms of the infection. On the 133d day after infection the animal was autopsied and from it were recovered many immature worms which had the delicacy of females, but in other respects were similar to immature males. Acetabula and gynecophoral canal were diagnostic of males, but no internal differentiation of organs could be made out. No worms of a definite female form or type and no mature males were obtained. In other experimental animals, both mice and dogs, infected with cercariae from both Japanese and Chinese sources and allowed to live long past the time when maturity is expected for the majority of the worms (50 days, judging from the curve, Textfig. *C*), only one or two pairs of worms were found, while the greater part of the infection consisted of undersized worms, none of which in any respect approached maturity. It can hardly be believed that the worms failed to mature for lack of nourishment or because of crowding, since in much heavier infections all worms have been found to be mature or to be normally maturing. If one regards these worms as males, which is the most reasonable belief, then one may add the corollary that the absence of females in the one instance and paucity of females in the other cases is, in some way, correlated with the lack of maturity in the males. While it would be going too far to say that the presence or absence of females in these cases determines the maturity or lack of maturity of the males, we have examined no infection in which mature males were found and female worms were absent.

In most of these infections in which only immature male specimens were recovered the cercariae came from a single snail. In most of the other infections, where both male and female worms developed normally to maturity, the cercariae came from three or more snails. Our

evidence preponderates, then, in favor of the belief that cercariae from a single snail host are frequently (although not necessarily) unisexual. In this we are merely arriving at the same conclusions as Fujinami, Cort and others.

The mature Schistosoma japonicum.

The mature state obtains when the sexual organs are able to function properly and fertilized eggs are passed. Pairing is no criterion for maturity in this species, since mating has been observed in some cases ten to twelve days before sexual maturity has arrived. In experimental animals some worms, in an infection, mature before the thirtieth day, for viable eggs first appear in the stools about that time (young dogs). Allowing for a short period of time for the passage of the ova from the point of deposition in the gut wall to the lumen of the gut, we reckon that the minimum time from invasion of the host to maturity of the worm is approximately twenty-eight days. Since larger experimental animals do not show eggs in the feces until near the end of a five-weeks infective period, it seems likely that this period is more nearly correct than if the estimate were placed earlier.

Comparing the interval between the nineteenth and the thirtieth days with the earlier periods of growth (Textfigs. *C* and *D*), one sees that actual recognizable development and differentiation occur more rapidly previous to the nineteenth day than at any time following it, so that the period between the tenth and the nineteenth days may be regarded as the chief growth period, while the interval immediately following this is probably one of internal maturity. On the thirty-first day the maximum range of any series of *Schistosoma japonicum* is practically as mature as it will become, but the mean average is far from being mature. The condition of maturity for the entire series does not obtain until after the seventieth day, when the maturity stage designated by us as "χ" has been reached. If reference is now made to Textfigure *D*, in which the growth in size is graphically represented, it is observed that the mean average length at thirty-one days is only about 3 mm., although the maximum male specimens may measure over 6 mm. ("χ" stage) and the maximum female worms over 7 mm. ("σ" stage). Thus it is seen that size is one of the criteria of sexual maturity. Thus maximum maturity practically obtains in the furthest developed of a series by the forty-first day, even though considerable growth takes place in these individuals up to the seventieth day. It is possible that size growth is temporarily halted by a precocious maturity and is resumed only after maturity has been attained.

Normal mature worms in the mesenteric veins reach a length of twelve mm. when relaxed, but an elongate specimen in these vessels may stretch to 30 mm. In a heavy infection the worms seldom lie alone, but are usually mated and occur in bundles of six to ten. Such groups may be present even in the minor radicles of the mesenteric veins. A census of one such group, in a mid-ileal sector, showed the presence of 12 pairs *in copula*, beside 11 separate males and 13 separate females. The worms are attached by their suckers to the endothelial lining of the vessel and, as far as our observations show, are headed against the blood current. Thus distention of the vessel is obtained, which makes it possible for them to work their way, no doubt, even into the capillaries. The movement of the worm is typically that of the trematode group, with alternate attachment by oral and ventral suckers.

Typically, both males and females show more extension when active within the vessels than in an isotonic nutrient solution *in vitro*. We have been able to keep them alive, however, in isotonic Locke's solution, at room temperature (24° C.), for fifty-six hours. In the females the longitudinal muscles are practically the only ones which are developed. In the males, in addition to the longitudinal series, those of the two suckers and of the gynecophoral canal are important. The male is typically figured and described as elongate cylindrical, with the gynecophoral canal deeply grooved out from the ventral sucker posteriad. It seems highly probable, however, that this is not a relaxed position. On bringing active worms into an anaesthetizing medium, such as one in which sodium chloride or magnesium chloride is slightly hypertonic, true relaxation results and the worm flattens and broadens, so that its shape is more like a Clonorchis or Eurytrema than like that of the ordinary schistosome.

The integument of the adult *Schistosoma japonicum* is relatively thin, but is resistant to pressure and to dilute solutions of acids or drugs. The entire integument is covered with minute, acuminate spines, which, however, are more conspicuous within the ventral sucker. The muscular elements of the male worm are particularly well developed. The oral sucker is set off from the rest of the body as distinctly in the adult worm, as in the cercaria, and has powerful muscles of several series to permit it to function properly. The ventral sucker is sunk deeply into the body so that its attachment to an object secures the worm as if it were a permanent holdfast. The ventrolateral musculature of the gynecophoral canal of the male is particularly well developed. When placed in an unfavorable medium both male and female worms roll up into a tight spiral.

The excretory system of the young larva within the mammalian host has been described through the ϵ stage (Fig. 26), when the two-fold dichotomy of the original four flame-cells and capillaries of each side (Fig. 23) has resulted in sixteen flame-cells for each side of the body. With the growth and maturity of the worm this bifurcation of the distal elements of the system continues. In immature specimens, on the eighteenth day after infection, this dichotomy was observed to have proceeded to a 5-fold condition, so that for each original flame-cell thirty-two cells have resulted, making the total for each side of the body one hundred and twenty-eight. These cells have become much smaller than the original cell elements. In adult worms we have not been able to make out the exact pattern, but a study of typical regions indicates that a further dichotomizing has taken place. The formula of the adult worm is, therefore, a simple one, namely $2\ (2)^n + 2\ (2)^n$ for each side of the body, where n represents the number of divisions that has taken place, if one takes the pattern of the β stage (Fig. 23) of the schistosomulum as the basic or least common denominator. If the condition in the immature cercariae (Fig. 19) is considered as fundamental, the formula becomes $(2)^{n+1} + (2)^{n+1}$. If this is, in turn, referred to the most primitive condition in the cercaria (Fig. 18), when only a single flame-cell is found on each side of the body, the formula is still further simplified and becomes: $(2)^{n+2}$, or $2\ (\alpha)^{n+1}$, in which α represents the fundamental pattern of division which has become impressed on the worm.

In the adult excretory system the bladder is a small triangular receptacle with a postero-dorsal pore and antero-lateral collecting tubules. These tubules, as well as the secondary canals, are ciliated. No excretory concretions have been observed by us within the system.

The gut in the mature *Schistosoma japonicum* is a simple structure. Immediately behind the oral sucker is a group of esophageal glands which are first present at an early stage (ϵ stage, Fig. 26). The esophagus extends to the pre-acetabular region where it bifurcates to form the two ceca. These run an undulating course posteriad about three-fifths the length of the worm, when they again unite and continue to the subdistal region of the worm as a single cecum. In all specimens taken from the portal system (on the third and succeeding days after infection) the gut is found to be filled with dark brown material. Among other substances ingested are many red blood corpuscles. It seems likely that some of this pigment is the degeneration product of red blood cells. It seems equally probable that red blood cells comprise a large share of the food material of the worms. The fact that

the worms appear to mature only in the portal system has lead us to believe that there must be some food substance in the blood coming from the gastro-intestinal tract which is not present in the blood of other veins, and which makes it possible for these worms to live and mature only in this locality. Thus far, however, our evidence does not warrant any dogmatic statement in connection with this important biological fact.

We have made no special study of the nervous system of the adult *Schistosoma japonicum*, but those observations which we have made agree with those of Lortet and Vialleton (1894) and Looss (1895) on the related Egyptian forms.

The generative organs of the adult worms have been described and figured in detail by Katsurada (1904: 6–10), Fujinami (1907) and Miyagawa (1916), although most of this information is in the Japanese language. It is not our purpose to restate the details of structure which are well described and well known.

In the female the multiple vitellaria occupy the posterior two-fifths of the body, while the elongate ovary lies just behind its middle. Fujinami's figure (l.c., Taf. 2, Fig. 14) shows the critical relations admirably, with the oviduct arising from the posterior end of the ovary, then reflexing on itself toward the ootype which lies in front of the ovary. The vitelline duct, likewise, comes in from the posterior region while the ootype is surrounded by small goblet-shaped shell glands. The uterus lies just ahead of the ootype and consists of a long meandering tube which ends immediately behind the ventral sucker. It is filled with eggs which are hyaline near its proximal end, but become more and more yellow as the uterus approaches the genital pore. This is situated immediately behind the ventral sucker. We have been unable to find a seminal receptacle, but have frequently seen sperm cells making their way up the uterus against the outward flow of maturing eggs, and have traced them to the ootype, where they were found to be present when the egg shell was laid down. Actual fertilization of the oocyte frequently does not take place until the egg is near the genital pore. In such a position several sperm cells have been observed within the shell of the still unfertilized egg.

In the male the conspicuous genital structures are the testes. These lie almost immediately behind the ventral sucker, and, according to our observations, are constantly seven in number. There is a tendency toward transverse lobation in the testes. This peculiarity might lead the observer on superficial examination to regard each lobe as a distinct testis. A typical sagittal section through the region of the testes

of *S. japonicum* is shown in Photomicrograph 43. On the anterior dorsal aspect each testis becomes drawn out into a short tubule, the vas efferens. All seven tubules communicate with a common collecting tubule, the vas deferens, which proceeds anteriad, enlarging to form a seminal vesicle. In the median frontal plane, just behind the ejaculatory duct, there is a ventral outlet to the genital opening. We have found no cirrus sac. The genital orifice is enlarged at the time of copulation, and is applied to the female genital orifice for the transfer of sperm.

In a group of mature specimens of *Schistosoma japonicum* in which the sexes are approximately equal, most of the worms will be found in copula, with the female enclosed within the folds of the gynecophoral canal of the male. The anterior and posterior ends of the female are frequently found extending outside the canal of the male. The worms are usually mated head to head, although we have observed the reverse condition to obtain in a few instances. It seems highly improbable that worms, seen paired, are always in copulation. In fact in the frequent serpentine coiling of the female within the gynecophoral canal (Fig. 33) copulation is impossible. However, in view of the absence of a seminal receptacle in the female, where sperm may be stored, fertilization depends on the constant attendance of the male on the female. The lack of such a condition probably explains the occasional presence of unfertilized eggs in the feces in batches of fertilized ones.

Spermatogenesis in Schistosoma japonicum.

(Figs. 34 to 61; Photomicrographs 44 to 52.)

In view of the work of Lindner (1914) on the spermatogenesis of *Schistosoma haematobium* it seemed advisable to inquire into the maturation and division phenomena of the male germ cells of *S. japonicum.* For this purpose material fixed in corrosive-sublimate-acetic or formalin was found to be unsatisfactory, so living adult male worms from experimentally infected dogs were fixed in Flemming's stronger chrom-acetic-osmic fluid and, after due technic, were stained in iron-alum-haematoxylin, and were then mounted in neutral damar in xylol. The sections were cut eight microns thick along the median sagittal plane, so that the maximum number of maturing sperm cells would be seen in one section. All of the stages of development could then be observed in a few sections. The majority of sperm mother cells were found near the cortex and the more mature cells toward the center of the testis, but this condition was not constant.

In the ordinary immature male germ cell the nucleus is spherical to ovoid (Fig. 34; Photomicrograph 44) and contains a large number of chromatin masses strung on a net-work of achromatic fibres. In addition, there is a large centrally placed nucleolus of dense homogeneous material. As this sperm mother cell prepares for maturation the nucleolus disappears (Fig. 35; Photomicrograph 45) and the chromatin granules come to lie in a single tightly coiled spiral chain (Figs. 35, 36; Photomicrograph 46), which at first becomes more tightly coiled and then breaks up into a number of discrete bands, with the chromatin element arranged at intervals along the band. These bands then revert to an achromatic threadwork on which the chromatin elements become arranged (Figs. 37–39; Photomicrograph 46). It is during this period, following the spireme formation and preceding the disappearance of the achromatic fibrils, that syndesis takes place. For, while fifteen distinct chromosome elements could be counted as the phenomenon was about to take place (Fig. 38), only eight could be found at the conclusion of this stage. With the next stage (Figs. 40, 41) internal division is observed to have been completed, so that seven tetrads and one diad may be observed. After a preliminary pairing (Fig. 42) of the chromosomes, the spermatogonial division takes place (Fig. 44; Photomicrograph 48), resulting in a qualitative separation of chromosomes. Seven bivalents go to one pole and eight bivalents go to the other pole. In the latter group (Photomicrograph 49) is the heterosome containing the "X" members. It was observed that this chromosome reached the pole earlier than the other chromosomes. Thus two primary spermatocytes have resulted from the spermatogonial division, one of which has seven autosomes (Figs. 48, 49), while the other has seven autosomes and one heterosome (Figs. 45–47), and the division is reductional.

The qualitative division is followed by the quantitative or equational division. A pair of primary spermatocytes, in the process of division, is seen in Fig. 50. The early telophase of the division is at hand. Seven chromosomes can be counted at each pole of the upper cell, while eight can be counted at each pole of the lower cell. The earlier equatorial plate of the lower cell is seen in Fig. 51. Here the "X"-chromosomes are observed to have preceded the ordinary chromosomes to the poles. The completed secondary spermatocytes are shown in Photomicrographs 50 and 51. The four secondary spermatocytes, resulting from the two divisions of one spermatogonium, are usually close together. Figures 52 to 55 and Photomicrograph 52 represent one such group of secondary spermatocytes, two of

which have seven univalent autosomes and two have seven univalent autosomes and one univalent heterosome.

Separation of the secondary spermatocytes may be accomplished soon or the cells may remain attached for a time (Fig. 56). In the meantime the nuclear elements of each soon become condensed and the cytoplasm becomes absorbed. Thus there results the spermatid (Figs. 57 to 60), and shortly following this the differentiation into the spermatozoon (Fig. 61).

The observations on the spermatogenesis of *S. japonicum* follow those of Lindner on *S. haematobium* very closely and agree with his studies point for point, except that the reduced number is respectively 8 and 7, instead of 8 and 6, indicating a specific difference in the chromosome complex of these two related species. While information is not at hand in either of these studies, as to which group constitutes the female and which group constitutes the male chromosome complex, comparative evidence preponderates in favor of the view that the larger number designates a female cell.

Summary.

A. The egg-miracidium phase of the life cycle.

1. The fertilized egg of *Schistosoma japonicum, in utero,* is a lenticular, ovoid object, about 67 by 50 μ in size, and bears a more or less pronounced spine on one side near the anterior end.

2. The egg of *S. japonicum,* found in the feces, is an oval object with an average length diameter of 89 μ, while the breadth diameter averages 66 μ. The most satisfactory basis for calculating relative sizes of these eggs is a comparison of the product of the three diameters. Measurements of 500 mature schistosome eggs from infected dogs gave a unimodal curve of size distribution, with wide limits, but a small standard deviation (i.e., $\pm$ 1.5).

Measurements made by other observers show wide differences, which cannot be accounted for entirely on the basis of host, but depend, in part, on the actual maturity of the egg measured. Such measurements are not accurate indices of the egg-size, since they do not allow for the third dimension.

3. The egg of *S. japonicum,* as found in the feces of infected animals, usually contains a mature or nearly mature miracidium. In addition to a simple, but efficient excretory system of four flame cells and connecting tubules, the miracidium contains anteriorly an undifferentiated, sacculate gut with granular contents and four nuclei. Lateral to the gut is a pair of granular secretory glands with oxyphilic reaction,

while posterior to the gut is a dense mass of glands with clusters of ducts opening laterad. These latter exude from time to time a mucoid material of basophilic reaction. The larva is thus provided with secretory glands of both basophilic and oxyphilic reaction which are probably endowed with proteolytic powers. The germ balls are developed from a generalized germinal mesothelium. Whatever nerve cells are present in the miracidium are found in a central mass with 6 anterior and 6 posterior trunks connected with transverse commissures, just ventral to the basophilic secretory glands.

4. The cilia of the epithelium consist of two groups, an anterior set with cilia graduated off toward the cephalic end, and a posterior set covering the remainder of the organism. The latter are of equal length, undifferentiated, and rather far apart, while the former are close together and have a decided differentiation, particularly in the posterior elements. The animal is, therefore, heterotrichous.

5. The phenomenon of hatching is based on two sets of factors, internal and external. Of the former, maturity of the miracidium and increased internal tension are the most important, while hypotonicity and absence of fermentative agents in the medium are the most important of the latter group. Hatching takes place under rather wide limits of temperature. Acidity of the medium soon destroys the larva.

6. The miracidium escapes through a longitudinal split in the shell, usually opposite the spine. After adjusting itself to the medium the larva ascends to within a few millimeters of the surface, where it swims around in a typical fashion during a period of 60 to 72 hours, which period may be termed the *infective stage*. The movement is that of a free-living organism, with a rapid, straight, forward glide, while it is deflected from its path by any small object, in which event a reversal of direction is effected by a turn-table method. During this active period the animal is a slim elongate object.

7. The *post-infective period* is one of senescence, during which the miracidium moves about slowly through the water, gradually settling to the substratum as the stored-up energy becomes exhausted. At this period the larva is oval and flattened.

8. In case the miracidium of *S. japonicum* comes in contact with the specific mollusc hosts, *Katayama nosophora, K. formosana, Oncomelania hupensis*, and probably other closely related species, it becomes positively attracted to it, and within a short time (varying up to several minutes) attacks the part with which it first comes in contact. Thus a whole colony of miracidia may be almost entirely eliminated from the water by the presence of a few of these molluscs. Although snails con-

taining one infection may be reinfected, it seems necessary for a certain time to elapse before such reinfection is possible.

9. Analysis of attempts to experimentally infect thirty *Katayama nosophora* with one miracidium each showed that in the first half-hour 9 of these penetrated the foot of the host, 8 penetrated the head and neck, 6 entered the mantle cavity, and 7 disappeared under the body. Of this number 7 were found on subsequent examination of the water, giving a maximum percentage penetration, under controlled conditions, of more than 76.

10. Infection of the snails with miracidia of *S. japonicum* occurs in the upper few millimeters of the water, which probably indicates a delicate adjustment of the phenomenon of infection to the habits of the snail, namely its position at or near the surface of the water.

B. The developmental cycle of Schistosoma japonicum within the mollusc host.

1. The course of the fluke has been traced through the snail for a period of 47 days, while these experimentally infected animals have been compared with naturally infected specimens containing mature cercariae.

2. The miracidium penetrates the snail at the point of contact by a head-on boring motion. The mechanical process is aided by the secretion of supposedly proteolytic substances from the two types of secretory glands of the miracidium.

3. Entrance may be effected (1) through the direct route, i.e., by penetration of the gill filaments and direct entry into the blood stream, or (2) indirectly, by boring through the tissues of head or foot, thereby gaining entrance to lymph sinuses. Actual penetration through the superficial tissues occupies a period of only a few minutes.

4. The proteolytic glands are present up to about the fifth day.

5. From about the seventh day the larva loses its differential characteristics and elongates. Meanwhile the worms slowly work backward from the anterior part of the head or foot through the lymph spaces surrounding the salivary glands to the region of the nephridia.

6. After three weeks the larvae have become elongate, spinose sacs, about 25 x 100 μ in measurement, and contain within the body cavity the morula stage of the secondary sporocysts. Soon after this some of them reach the lymph spaces, still further distad.

7. By the beginning of the fifth week the larvae have become definitely differentiated into primary sporocysts, reaching 400 μ in length and containing elongating secondary sporocysts Some of these have reached the lymph spaces near the liver.

8. At the beginning of the sixth week practically all of the worms have reached the lymph spaces between liver and gonads. By this time the primary sporocysts have ruptured, setting free the secondary sporocysts, while these latter in turn contain the germ balls of the cercarial generation.

9. At the end of seven weeks the secondary sporocysts measure 40 x 250 μ and contain cercariae with differentiating tails.

10. While the larvae, which gain entrance to the snail by the direct route, reach the liver much sooner than the other group, they mature no more rapidly than those which use the more circuitous path. Contrary to common belief this latter group are able to secure nourishment from the tissues through which they pass previous to their entry into the natural lymph spaces of the mollusc. In the case of the miracidia of *Schistosoma japonicum*, many more larvae gain entrance through the indirect than through the direct route.

11. Final differentiation of the cercariae takes place in the lymph spaces of the distal part of the snail. The parasite never breaks through into the hepatic or gonidial tissues except by accident, but remains bathed in the inter-lobular lymph sinuses, which become more and more distended as differentiation takes place.

C. The cercaria stage of Schistosoma japonicum.

1. While Japanese investigators first described the cercaria of *Schistosoma japonicum*, the first accurate detailed account of the larva was published by Cort (1919).

2. On reaching maturity within the parent sporocyst in the liver of the snail the cercariae erupt spontaneously, and come to lie in the surface film over the mouth of the snail. These eruptions occur sporadically as the motile larvae mature and outgrow their intra-molluscan domicile.

3. Movement on the part of the cercariae consists of four distinct types: (*a*) the nervous, jerky motion of the body with the ventral sucker as a pivot, usually observed in individuals at the surface film; (*b*) the free-swimming movement in which the caudal furci serve as anterior propellors; (*c*) the sinking movement; and (*d*) the "measuring worm" movement.

4. Variation in measurements of the cercaria is due (*a*) to differences in maturity; (*b*) to contraction and extension of the body and tail of the larva, together or separately; (*c*) to differences in nutrition, as well as (*d*) to intrinsic size variation.

5. The excretory system is constant for all species of mammalian

schistosome cercariae studied. It is, therefore, of generic and not specific value in diagnosing species of cercariae.

6. The cephalic glands consist of five pairs of cells with contents similar to each other. These glands differentiate early. When first observed in very young cercariae they are mucoid in nature and basophilic in reaction. As maturity is reached they change from basophilic to oxyphilic, which condition prevails in the mature cercaria.

7. The hollow boring spines which crown the openings of the cephalic gland ducts function in drilling microscopic holes through the skin of the invaded mammal. This process is probably accomplished the more easily because of the proteolytic ferments which are poured out through the duct openings and digest away host tissue.

8. The genital *anlage* is undifferentiated in the cercaria.

9. Viable cercariae cover a range of individuals all the way from those which have not yet taken up locomotion to those that have been free-swimming for 30 or more hours. Decaudation *per se* does not hinder viability, since infection appears to result more from the contact of cercariae in the surface film than from the active swimming movement of the cercaria.

10. The post-infective stage is a short period during which the cercaria becomes senescent, loses its activity and degenerates.

D. The development of Schistosoma japonicum within its definitive host.

1. All of the developmental stages of the Oriental blood-fluke from the time of penetration of the cercaria to the sexual maturity of the worms in the portal system have been studied. A continuous series of twenty-four stages has been recognized. For convenience in reference it is proposed to use Greek letters from α to ω inclusive to refer to these stages. Determination of these stages is based on growth and maturity. Stages α, β, γ, δ and ϵ have not been previously described. Stages ζ and η to ψ (male) correspond in practically all respects to Cort's stages 1 (F. or M.) and 2 (M.) to 18 (M.). Only the earlier part of Cort's series 2 (F.) to 11 (F.) agree stage for stage with our series.

2. The earliest stage (α) was found in peripheral lymph nodes (inguinal lymph nodes of the mouse, 51½ hours after infection, and in the popliteal lymph nodes of the rabbits, 23 hours after infection). The second stage (β) was recovered from the inguinal lymph nodes and lung irrigations, 51½ hours and 70 hours after infection of mice, and 45½ hours after infection, from the popliteal lymph nodes and lung irrigations of rabbits. All later stages were recovered from liver irrigations, while β to ϵ stages were obtained from the other organs as follows:

Stage.	Animal.	Day after infection.	Organ.	Technic.
β	Mouse	2, 3	Inguinal lymph node	Dissection
"	"	2, 3, 4	Lungs	Irrigation; dissection
"	"	3, 4, 5, 6	Pleural cavity	Washing
"	Rabbit	2, 3	Popliteal lymph node	Dissection
"	"	2	Lungs	Irrigation; dissection
"	"	4	Mesenteric vessels	Irrigation
γ	Mouse	3, 4, 5	Lungs	Irrigation; dissection
"	"	4, 5, 6	Inguinal lymph node	Dissection
"	"	4, 5, 6	Pleural cavity	Washing
"	Rabbit	3	Popliteal lymph node	Dissection
"	"	3, 4	Lungs	Irrigation; dissection
"	"	3	Mesenteric vessels	Irrigation
"	"	3, 4, 5, 6	Pleural cavity	Washing
δ	Mouse	5, 6	Lungs	Irrigation; dissection
"	Rabbit	5, 6	Mesenteric vessels	Irrigation
"	"	4	Capillaries of legs	Irrigation
"	"	4, 6	Spleen	Irrigation
"	"	4, 5	Peritoneal cavity	Washing
"	"	4, 6	Pleural cavity	Washing
ϵ	Mouse	6	Lungs	Irrigation; dissection
"	Rabbit	5, 6, 7, 8	Mesenteric vessels	Irrigation
"	"	8	Peritoneal cavity	Washing
"	"	7, 8	Spleen	Irrigation

3. Growth of the young worm is dependent on several factors, among which the position in the host with respect to space and nourishment is all-important. Specimens found in lymph nodes on the fifth day after infection in experimental animals were degenerating. Specimens taken from the pleural washings of mice on the sixth day showed degenerative changes. Growth is correlated with the digestive ability of the worm and that in turn depends on the development of the gut. While red-blood cells of the host are commonly found in the young schistosome beginning with the β stage, digestive changes within the gut have not been noted until the worm arrives in the portal system. Maturity of males is apparently dependent on the presence of one or more females in the portal system.

4. Successive stages of development in experimental animals (mice, rabbits and dogs), furnish the basis for construction of a *Curve of Growth* for maturing *Schistosoma japonicum* in the definitive host. Starting with the α stage, the spread of the curve from minimum to maximum becomes rapidly fan-shaped, having a greatest spread from the fourteenth to the nineteenth day, from which time on until matur-

ity the spread becomes slowly less extensive. The series from dogs show slightly more rapid development than that in mice and rabbits, although at the end of the full developmental period the curves coincide.

5. Sex differentiation is recognizable from the sixth day after infection. Mating has been observed on the seventeenth day, although sexual maturity is not reached until thirty days after infection. After the twenty-eighth day the females mature more rapidly than the males.

6. The number of testes in mature males is consistently seven. The full number of chromosomes is fifteen. A study of stages in the maturing male sex cells shows that an accessory (X) chromosome is present. After parasynapsis seven tetrads and one diad have been observed. Reduction occurs here, so that one primary spermatocyte receives eight chromosomes, while the other receives seven. The X-chromosome is slightly excentric in position and precedes the other chromosomes to the pole. A second division results in secondary spermatocytes, half of which have 7 autosomes, while half have 7 autosomes and 1 heterosome. The former group are considered to be male cells, and the latter group female cells.

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DESCRIPTION OF FIGURES.

PLATE I.

The egg-miracidium phase of the life cycle.

1. Fertilized egg of *Schistosoma japonicum*, as deposited by the female worm.

2. Unfertilized egg of *S. japonicum* in the feces of an infected dog.

3, 4, 5, 6. Developing stages of the embryo within the egg shell.

7, 8. Maturing miracidia of *S. japonicum*. These stages commonly occur in the feces of infected mammals.

9. The mature miracidium of *S. japonicum*.

10. The post-infective stage of the miracidium of *S. japonicum*.

PLATE II.

11. Detailed drawing of the anatomy of the miracidium of *S. japonicum*.

PLATE III.

The intra-molluscan life cycle.

12. The miracidium of *S. japonicum* immediately after penetrating of the tissues of the mollusc host.

13, 14, 15. The developing first generation sporocyst of *S. japonicum*.

16, 17. The developing second generation sporocyst of *S. japonicum*.

18, 19. Developing cercariae of *S. japonicum*.

20. The mature cercaria of *S. japonicum*.

PLATE IV.

21. Detailed drawing of the anatomy of the cercaria of *S. japonicum*.

PLATE V.

The developing schistosome in the definitive host.

22. The α stage of the young schistosomulum within the mammal host.

23. The β stage of the young worm.

24. The γ stage of the young worm.

25. The δ stage of the young worm.

26. The ϵ stage of the young worm.

27. The ϑ stage of the young worm, showing male and female differentiation.

28, 29, 30, 31. Adolescent and maturing stages of the male and female schistosomula, representing respectively periods ι, μ, ξ and π of growth.

32. Pairing of male worm (stage ρ) with female worm (stage $_{\iota}$), preceding maturity.

33. Mature pair of *Schistosoma japonicum in copula*.

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Spermatogenesis.

34. Spermatogonium.

35. Pre-synaptic spireme.

36. Synaptic phase of maturation.

37, 38, 39. Post-synaptic phases of maturation.

40, 41, 42. Tetrad formation.

43, 45, 46, 47, 48, 49. Primary spermatocytes.

44. Anaphase of spindle plate of primary spermatocyte.

50. Daughter cells in telophase of secondary spermatocyte.

51. Metaphase of secondary spermatocyte, with accessory chromosome, preceding autosomes to the poles.

52, 53, 54, 55. Four secondary spermatocytes, derived from one spermatogonium.

56. Completed secondary spermatocytes.

57, 58, 59, 60. Maturing spermatids.

61. Mature spermatozoon.

Note. The reference line for each group of figures indicates the relative size of the figures.

DESCRIPTION OF PHOTOMICROGRAPHS.

PLATE VII.

1. Uterus of female *Schistosoma japonicum*, containing fertilized immature eggs. From mesenteric vein of dog. (Japanese material.) × 130.

2. Fertilized immature egg of *Schistosoma japonicum* showing yolk contents and lateral hooked spine. (Japanese material.) × 400.

3. Eggs of *S. japonicum* from bloody mucus of infected dog. (Japanese material.) × 120.

4, 5. Immature egg of *S. japonicum* from feces of infected dog. (Japanese material.) × 340.

6. Maturing stage of miracidium, showing mucoid deposit from lateral ducts between larva and shell. × 340.

7, 8. Mature eggs of *S. japonicum* from feces of infected dog. (Japanese material.) × 340.

9. Mature miracidium of *S. japonicum* within shell, somewhat compressed, showing secretions of mucoid from lateral ducts, and of granules from head glands. × 340.

10. Shell of *S. japonicum* egg from which miracidium has escaped. Note lateral spine. (Chinese material.) × 240.

11, 12. Escaped *S. japonicum* miracidia, free in water, swimming and quiescent. Note mucoid secretion from right lateral gland duct and thickened cilium anterior to the duct opening. (Chinese material.) × 300.

13, 14. Stained specimens of *S. japonicum* miracidia of infective and post-infective stages. The dark staining mass in each photograph is the neural mass, superimposed on the lateral glands. (Chinese material.) × 240.

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15. Miracidium of *S. japonicum* (Chinese material) within *Katayama nosophora* from Japan, thirty minutes after exposure. × 250.

16, 17. Immature first generation sporocyst of *S. japonicum* in lymph space of foot of *Katayama nosophora*. Seventh day after exposure. × 333.

18. Immature first generation sporocyst of *S. japonicum* in peri-esophageal lymph space. Eleventh day after exposure. × 333.

19. Immature first generation sporocyst of *S. japonicum* in lymph space of foot. Thirteenth day after exposure. × 333.

20. Immature first generation sporocyst within gill filament of snail. Fifteenth day after exposure. × 333.

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22. Developing second generation sporocysts within first generation sporocysts, in fleshy part of foot of snail. Twenty-fifth day after exposure. × 333.

23. Elongating second generation sporocyst within first generation sporocysts in perilobar hepatic lymph spaces of snail. Thirty-first day after exposure. × 333.

24. Second generation sporocysts free within peri-lobar hepatic lymph space of snail. Germ balls of cercaria developing within. Forty-third day after infection. × 333.

25. Maturing cercariae of *S. japonicum* in inter-lobar hepatic lymph spaces of snail. Seven weeks after exposure. × 365.

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PLATE IX.

27. Second generation sporocysts teased out of infected snail. × 64.

28. Free-swimming cercaria of *S. japonicum* which has erupted naturally from *Katayama nosophora*. × 500.

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29. The young larva of *S. japonicum* in the skin of experimental animal. (Japanese material.) × 250.

30. The α stage of *S. japonicum* from inguinal lymph node of the mouse, 51 hours after infection; elongated × 87.

31. The β stage of *S. japonicum* from lung irrigation of the mouse, 72 hours after infection; slightly elongated × 87.

32. The γ stage of *S. japonicum* from liver irrigation of the mouse, 96 hours after infection. × 87.

33. The δ stage of *S. japonicum* from liver irrigation of the mouse, 120 hours after infection. × 87.

34. The ϵ stage of *S. japonicum* from liver irrigation of the mouse, 144 hours after infection. × 87.

35. The ζ stage of *S. japonicum* from liver irrigation of the mouse, 168 hours after infection. × 87.

36. The η stage of *S. japonicum* from liver irrigation of the mouse, 192 hours after infection; *a*, female larva, *b*, male larva. × 87.

37. The ϑ stage of *S. japonicum* from liver irrigation of the mouse, 216 hours after infection; *a*, female larva, *b*, male larva. × 87.

38. The κ stage of *S. japonicum* from liver of mouse, 12 days after infection; *a*, female worm, *b*, male worm. × 87.

39. The μ stage of *S. japonicum*, showing immature worms 17 days after infection; *a*, female worm, *b*, male worm. × 38.

PLATE XI.

40. The π stage of *S. japonicum*, showing immature worms 23 days after infection; *a*, female worm, *b*, male worm. × 38.

41. Immature male (?) worm from infection in which no females were found; from mouse autopsied 133 days after infection. × 38.

42. Characteristic specimens of mature *S. japonicum* worms in copula. × 6.

43. Section through mature male *S. japonicum*, showing seven testes, with lobation in testis$_2$ which, in a tangential section, might be counted as two testes. × 66.

PLATE XII.

44. Section through testis of *S. japonicum*, showing spermatogonium (*a*) preparing for division.

45. Presynaptic and spireme stages in maturing spermatogonium of *S. japonicum*.

46. Synaptic stages of maturing spermatogonium of *S. japonicum*.

47. Post-synaptic stage of maturing spermatogonium of *S. japonicum*, showing tetrad (*td*). Highly magnified.

48. Spindle plate of first spermatocyte division, *S. japonicum*. Lateral view.

49. Primary spermatocyte with 8 chromosomes. Accessory chromosome (X) is excentric in position.

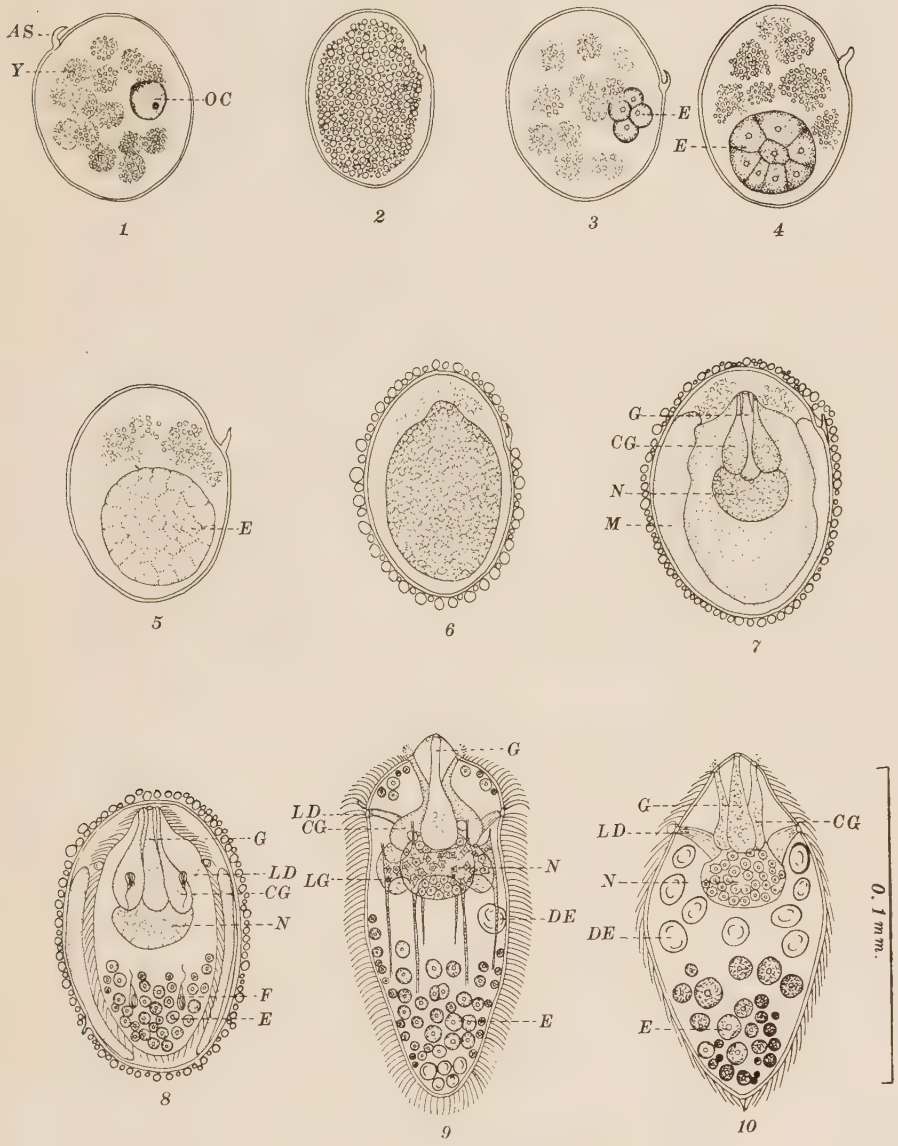
50. Primary spermatocyte with 8 chromosomes.

51. Secondary spermatocyte with 7 chromosomes.

52. Group of four secondary spermatocytes (*a*, *b*, *c*, *d*), two of which (*a*, *b*) have 7 autosomes and two of which (*c*, *d*) have 7 autosomes and a heterosome (X).

Explanation of Figures.

as,	abbreviated spine.
b,	excretory bladder.
bv,	blood vessel.
cg,	cephalic gland.
cp,	cephalic gland opening.
d,	cephalic gland duct.
de,	degenerate embryo or embryonic mass.
dl,	dorsal labium.
e,	developing embryo or egg.
ec,	embryonic cercaria.
eg,	esophageal glands.
ep,	excretory pore.
es,	embryonic sporocyst (2nd generation)
et,	excretory tubule.
f,	flame-cell.
g,	gut.
ge,	germinal epithelium.
h,	head gland.
i,	Island of Cort.
l,	liver.
ld,	lateral gland duct, "anterior duct" of authors.
lg,	lateral gland.
m,	mucoid secretion.
mi,	miracidium.
n,	nerve center.
nt,	nerve trunk.
o,	gut opening.
oc,	oocyte.
os,	oral sucker.
s,	sickle-shaped cilium.
sc,	schistosomulum.
sp,	sporocyst.
sp_1,	first generation sporocyst.
sp_2,	second generation sporocyst.
t_1–t_7,	testes.
td,	tetrad.
tt,	caudal excretory tubule.
v,	ventral sucker.
x, x_{I}, x_{II},	X-chromosome.
y,	yolk cell.



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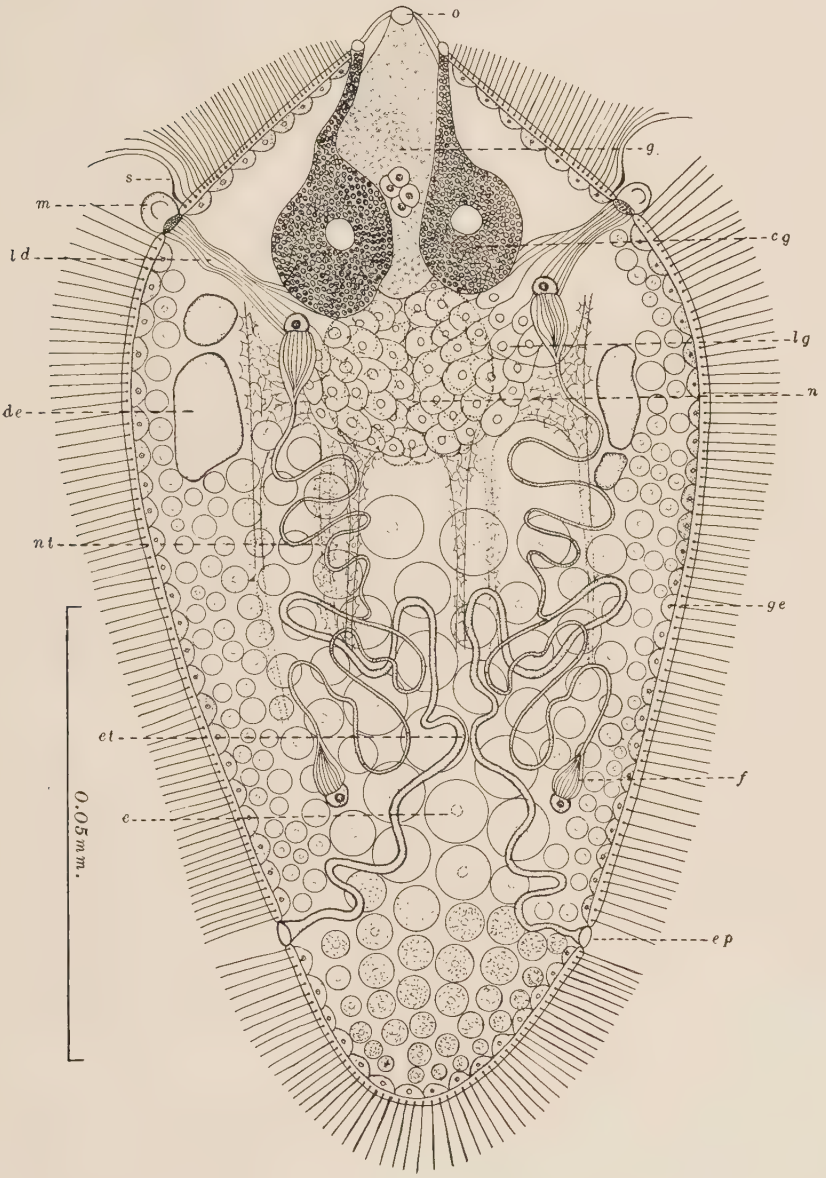

Fig. 11

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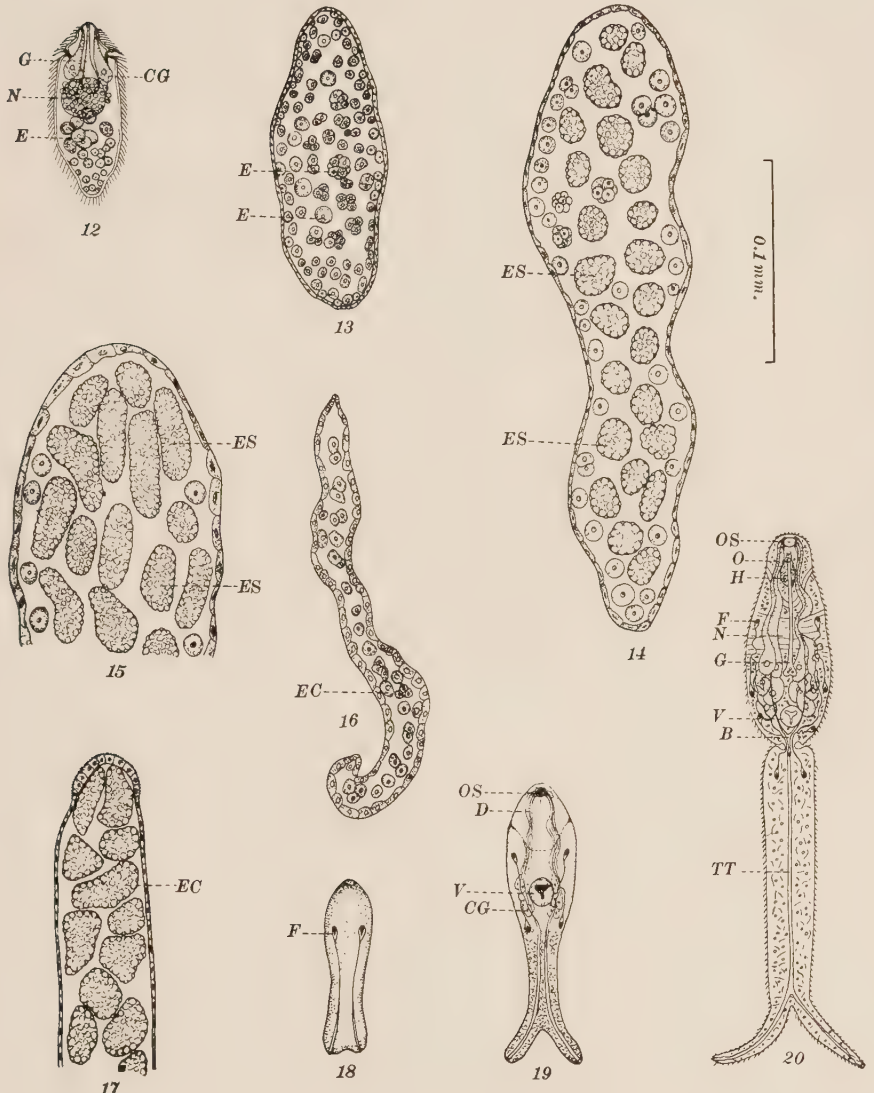

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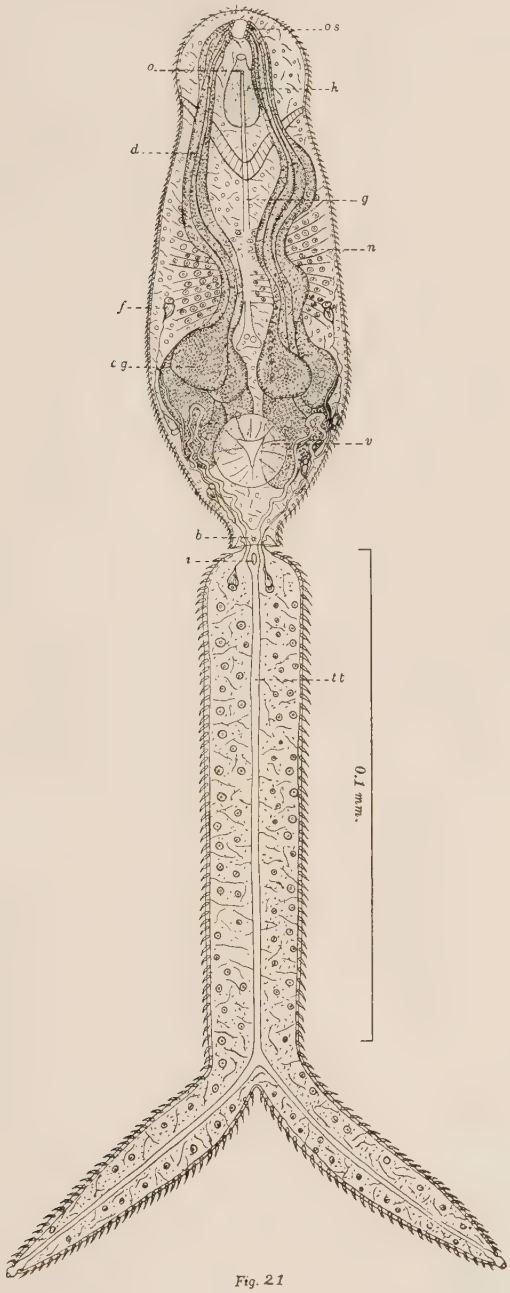

Fig. 21

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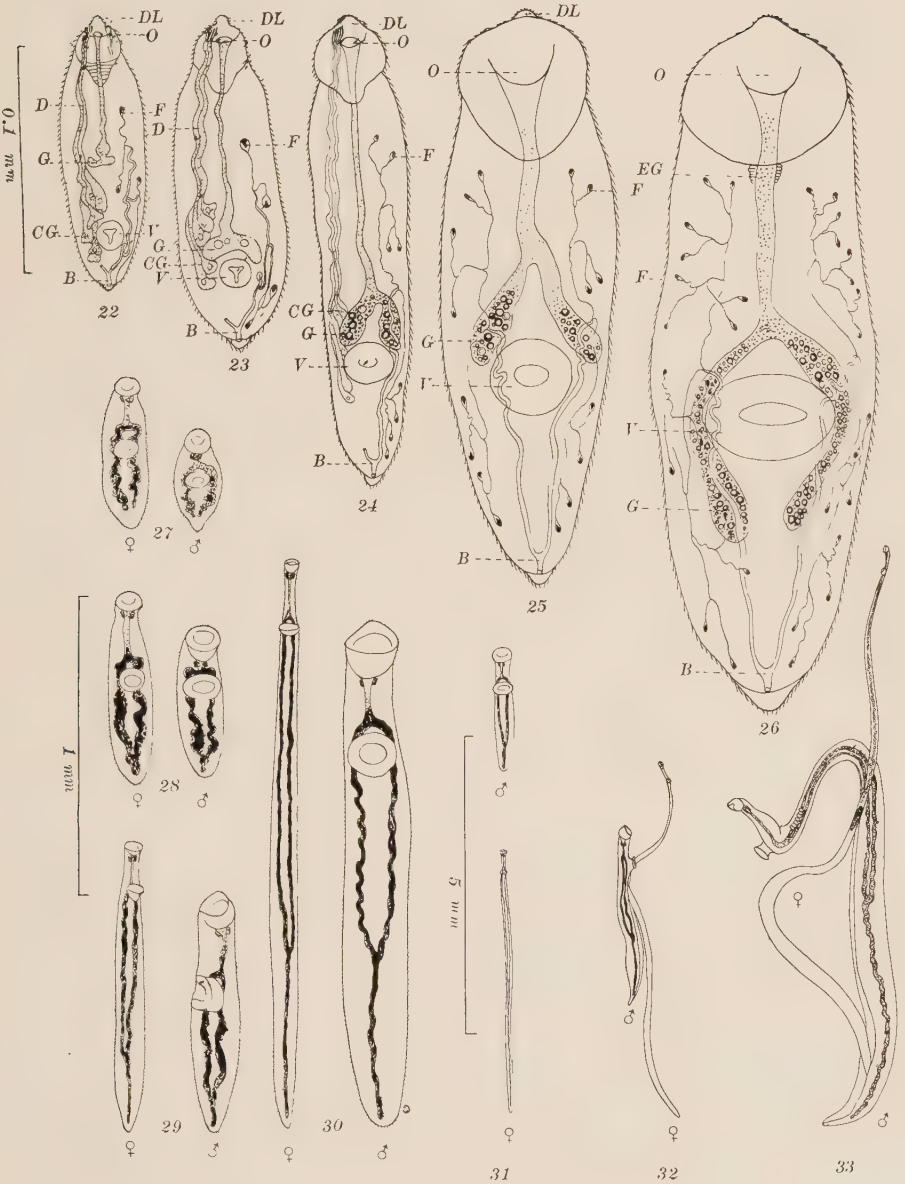

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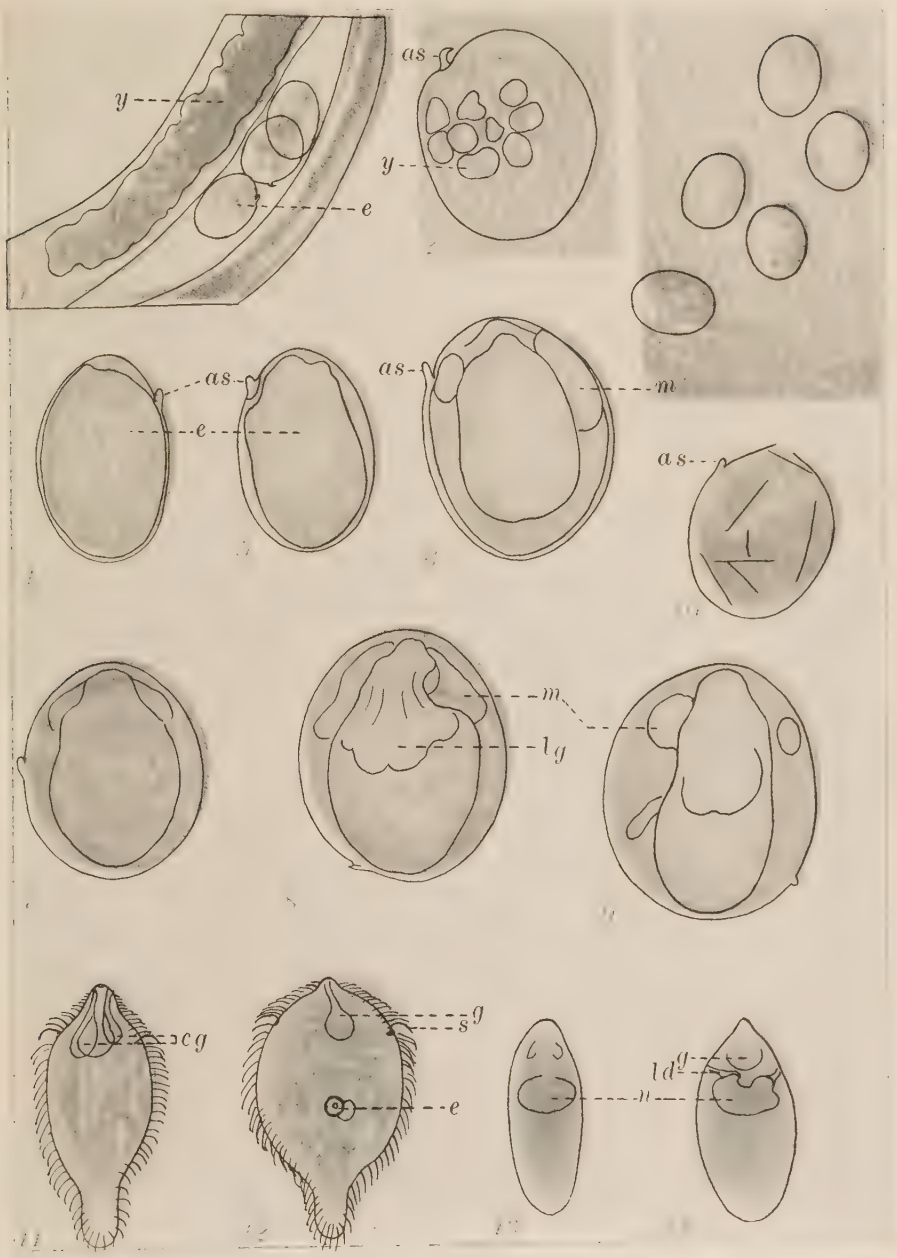
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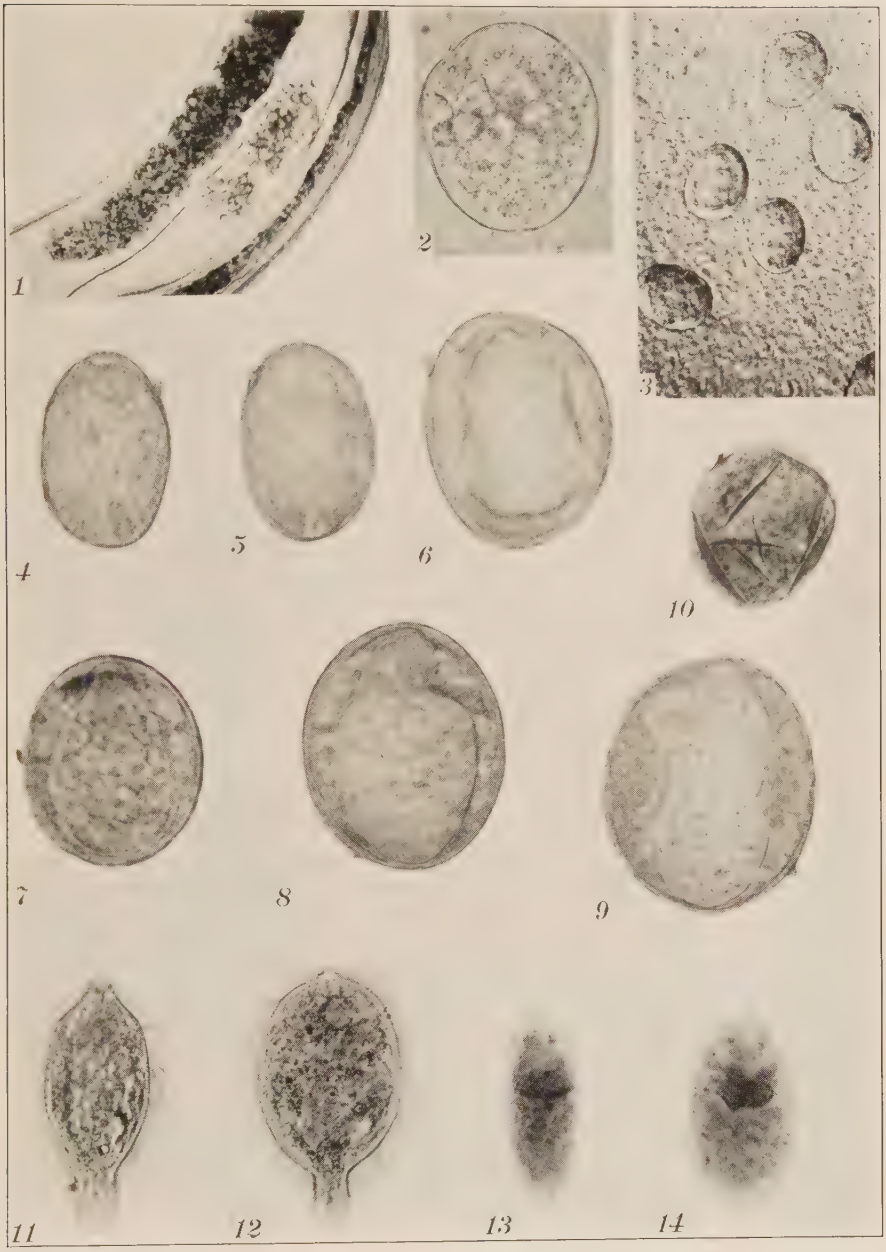

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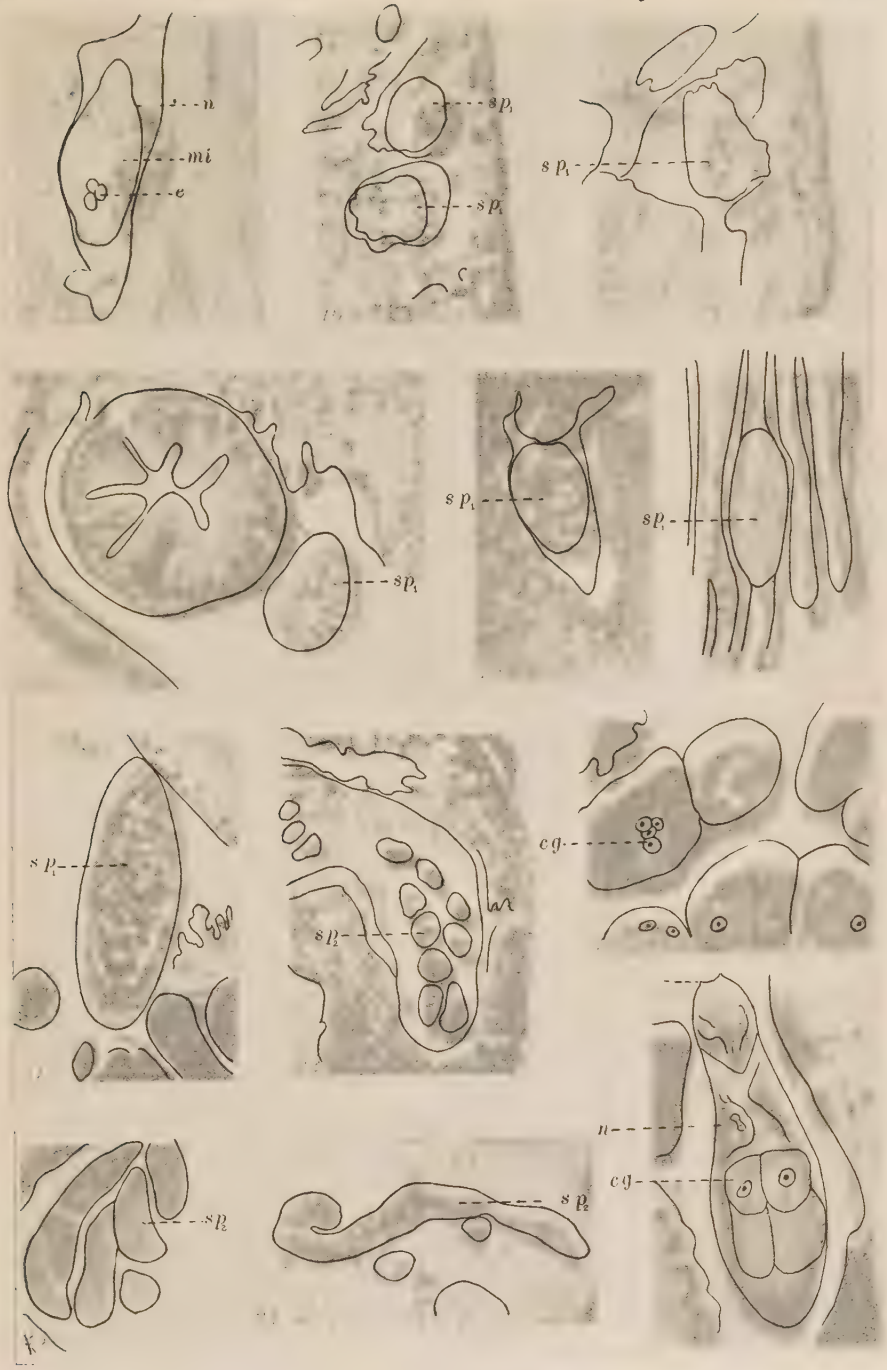

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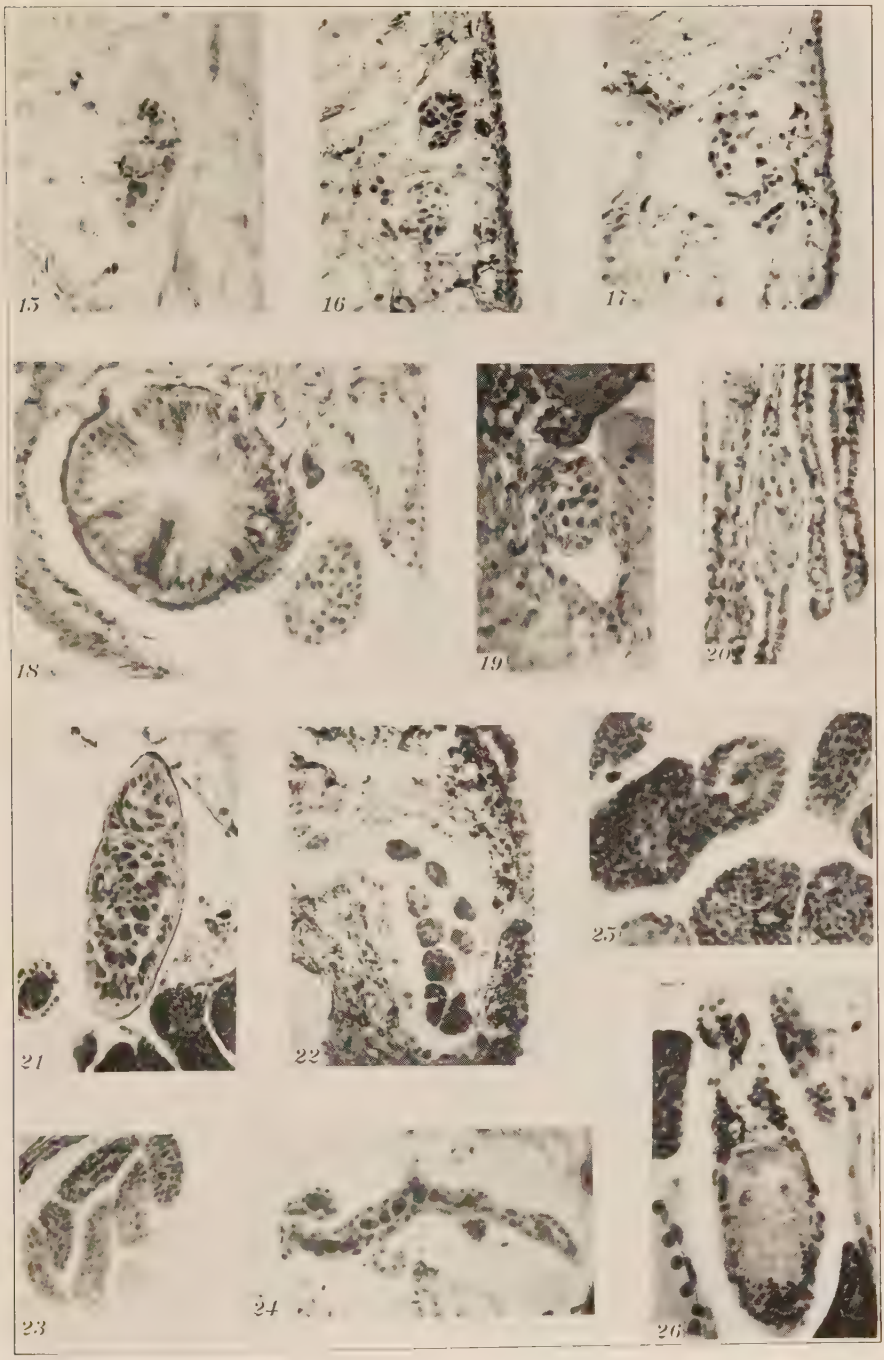

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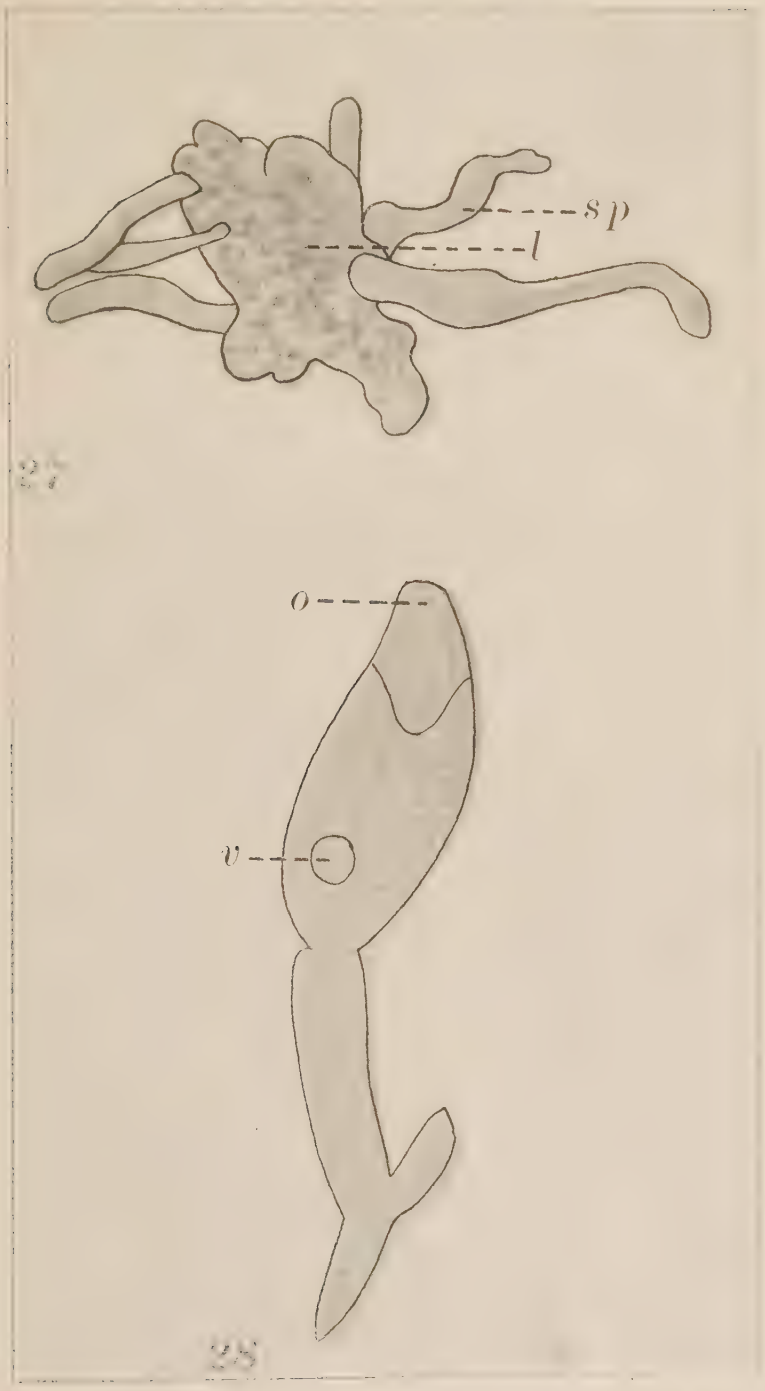

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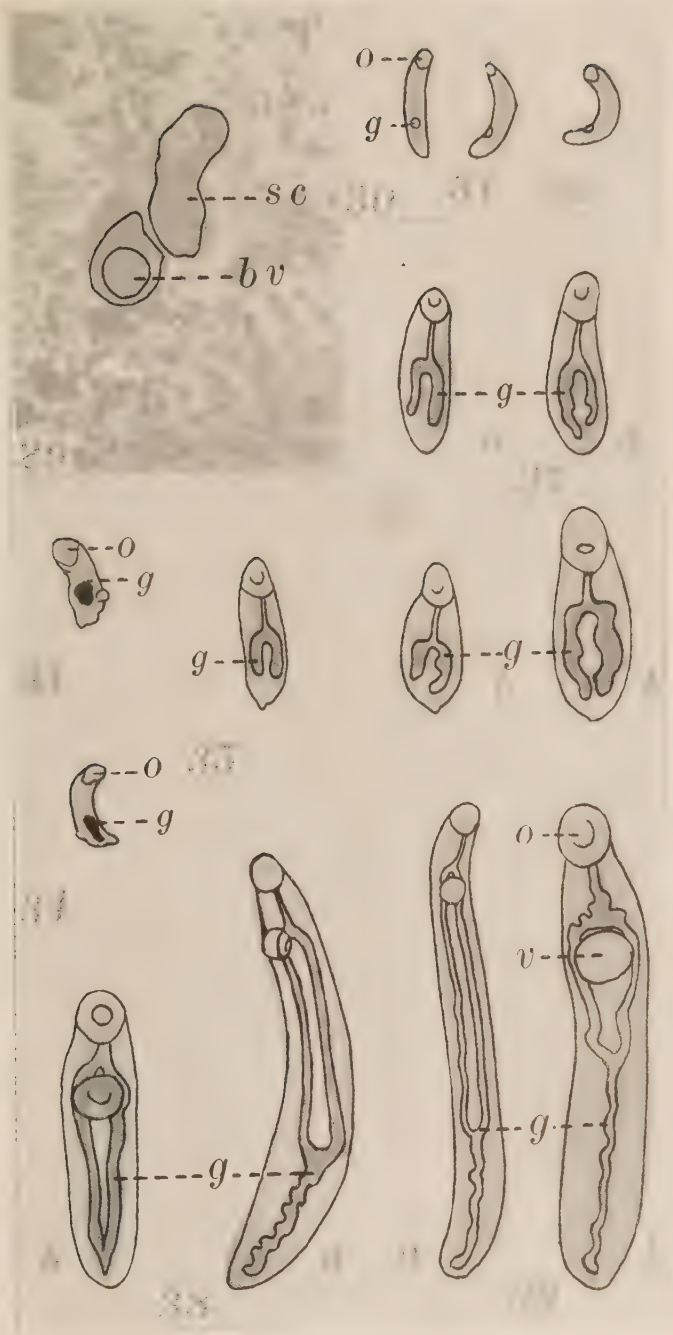
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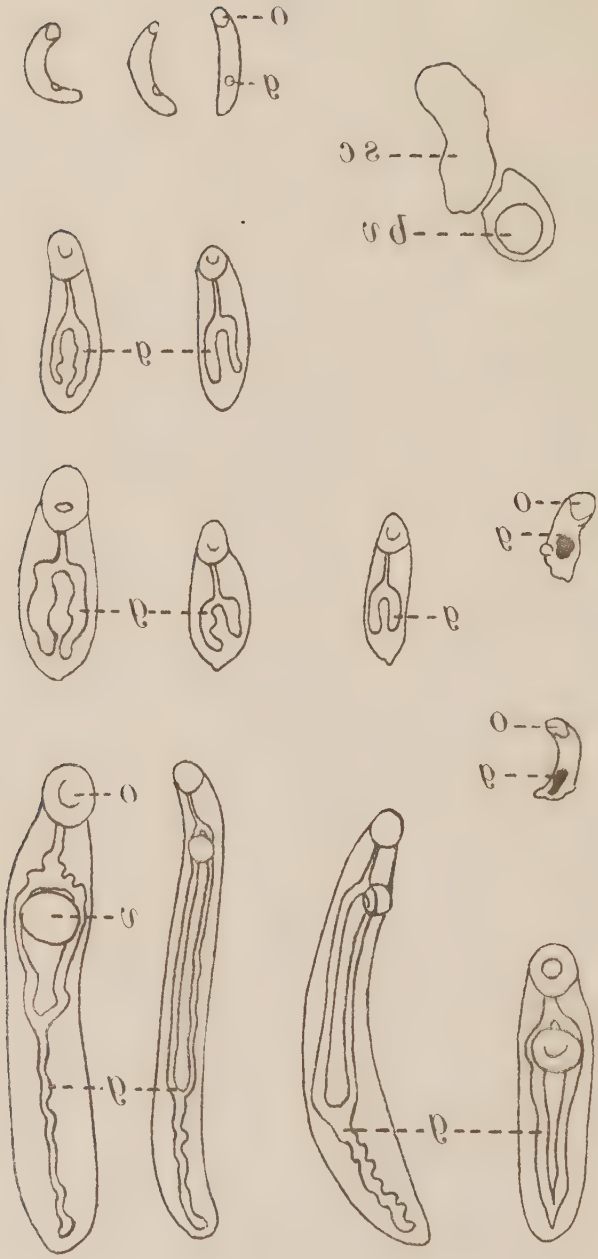

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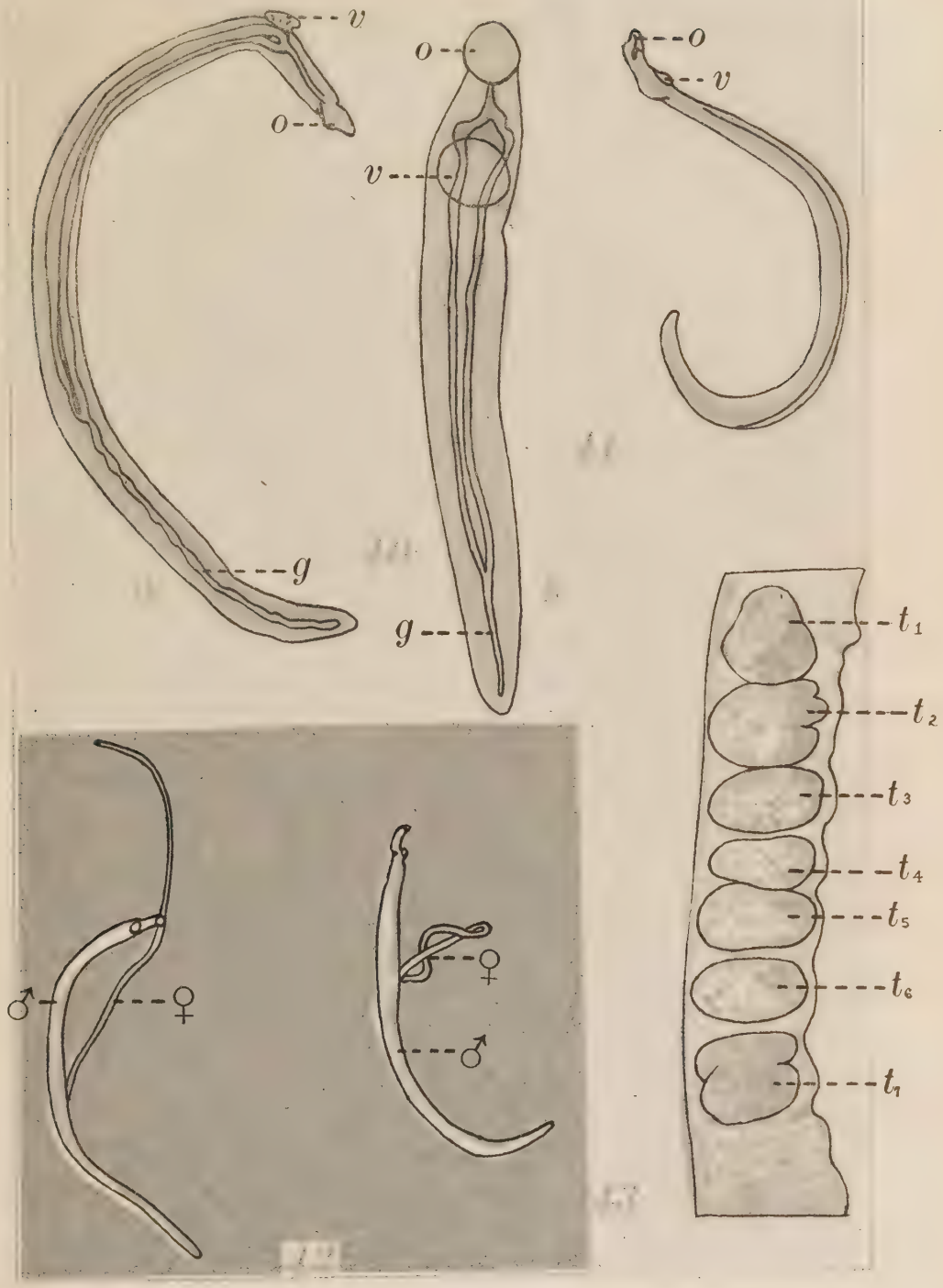

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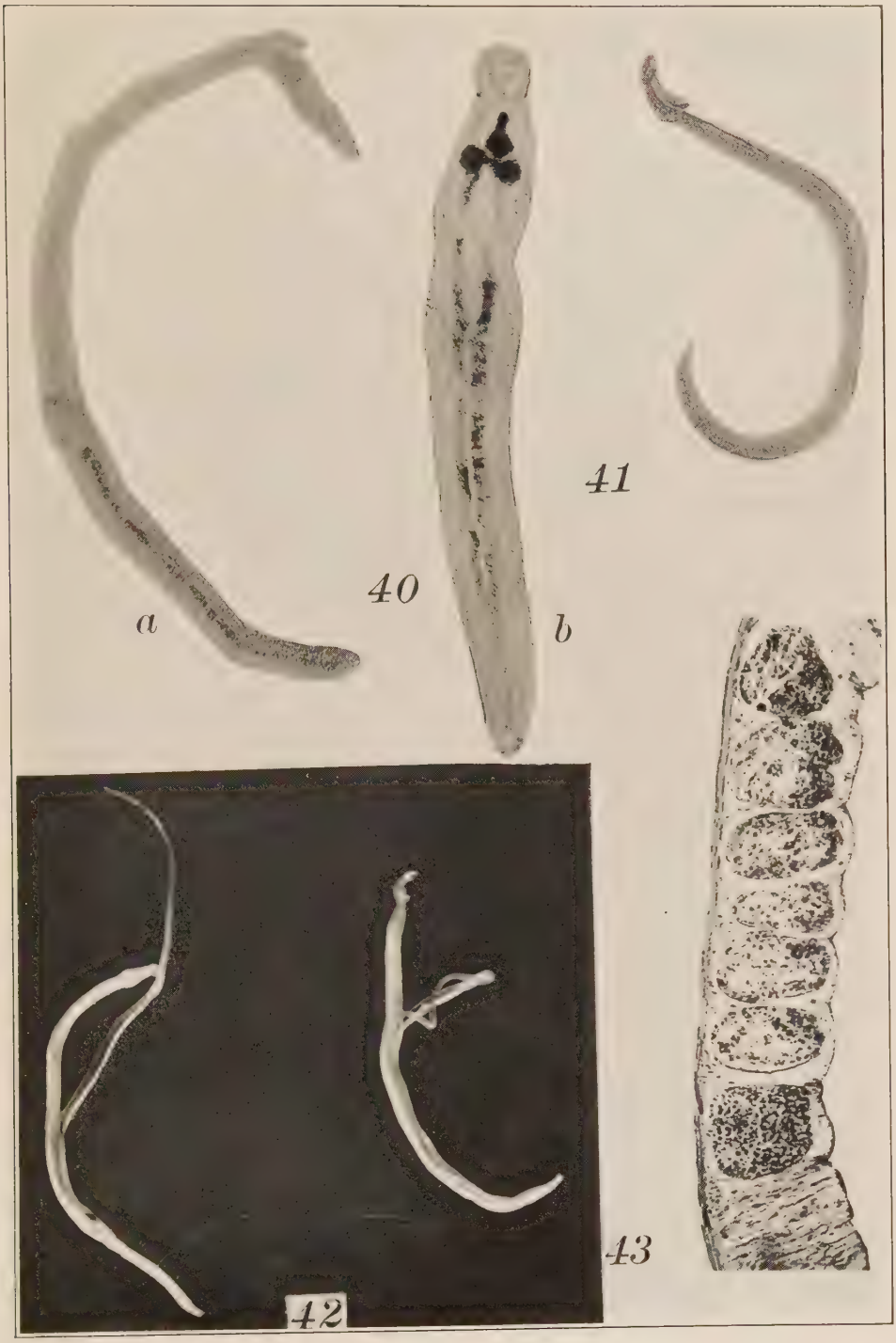

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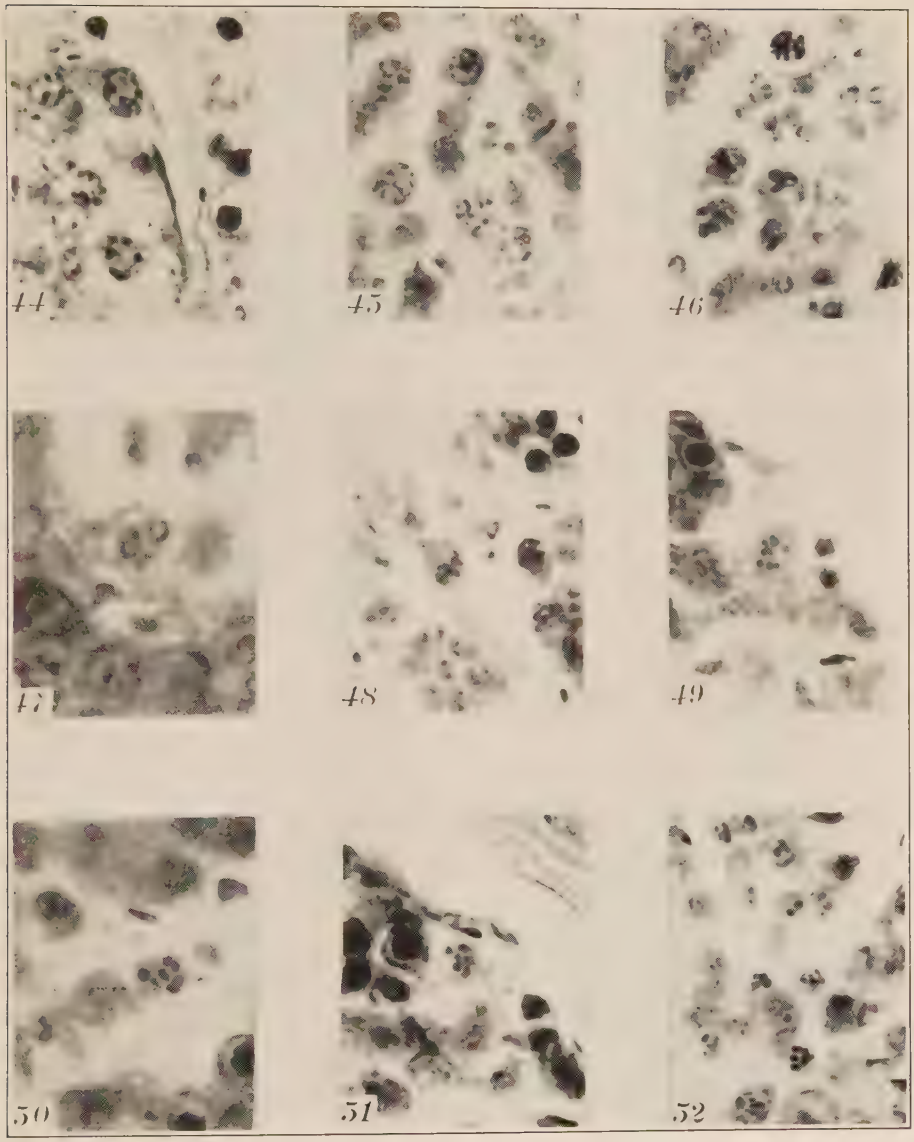

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III. THE ROUTE OF MIGRATION OF *SCHISTOSOMA JAPONICUM* IN THE BODY OF THE MAMMALIAN HOST.

(Plates XIII to XV.)

It was established by Fujinami and Nakamura (1909) that the skin is the principal portal of entry of *Schistosoma japonicum* into its mammalian host. Miyagawa (1913) demonstrated that the young worms invade the lymph and blood vessels and are carried by the blood stream through the right side of the heart to the lungs. He reasoned from this fact that the route taken by the worms from the lungs to their ultimate destination in the portal and mesenteric veins was probably also by way of the blood stream. He concluded, therefore, that the worms left the lungs primarily by the pulmonary veins, and were carried through the heart and aorta and mesenteric arteries to the capillary network of the gastro-intestinal tract, through which they worked their way into the mesenteric and portal veins. In a monograph on schistosomiasis in 1916, the same author stated that he had found young worms in the left side of the heart and in the capillaries of the kidney and intestine (Miyagawa 1916).

Narabayashi, however, after examining serial sections of young mice infected with *Schistosoma japonicum*, concluded that the worm took a different route from the lungs to the portal system (Narabayashi 1915, 1916). He found young worms in the pleural cavity, in the loose connective tissue of the mediastinum, and in the diaphragm, and therefore believed that the worm made its way out from the lung tissue into the pleural cavity, entered the mediastinum, passed through the diaphragm into the peritoneal cavity, and penetrated directly into the liver and portal vein.

Sueyasu (1920) confirmed Narabayashi's findings, except that he believed that the worm made its way directly through the diaphragm from the pleural cavity more frequently than it traversed the mediastinum.

Miyagawa, not satisfied with these conclusions, again took up the problem (Miyagawa and Takemoto 1921), and, following the experimental methods used by Narabayashi and Sueyasu, came to entirely different conclusions. Miyagawa and Takemoto reaffirmed Miyagawa's previous observations, that the principal route was entirely by way of the blood stream. These authors also successfully infected

three rabbits and a dog by direct inoculation of cercariae into the mesenteric artery, thus demonstrating that the cercariae could pass through the mesenteric capillary network into the portal system.

Because of the discrepancy between the conclusions reached by these two groups of Japanese investigators, we determined to repeat the work, using somewhat different methods.

Methods.

We used rabbits instead of mice in our first series of experiments, since the larger animals could be more accurately examined by gross methods, and were thought to represent more closely the conditions found in man. We used mice to check up our rabbit series and also for serial microscopic sections, where these were necessary for confirmatory evidence.

The method for our first rabbit experiment was suggested by the work of Ransom and Cram (1921) in determining the migratory course taken by *Ascaris* in the mammalian body. We immersed ten medium-sized rabbits in a large aquarium in tap water to a depth of about five inches. In the water we had previously placed the material from one hundred crushed specimens of *Katayama nosophora* which had previously been observed to be actively discharging the cercariae of *Schistosoma japonicum*. One rabbit nearly drowned and was therefore removed from the water after one and one half hour's immersion; the other nine rabbits were removed at the end of two hours.

One of these rabbits was killed each day from the first to the tenth day after immersion and was examined for the presence of young worms and for gross pathological lesions. The following technique was employed. The animals were killed by decapitation, so that as much blood as possible escaped from the body before examination. This blood, mainly from the carotid arteries, was collected in a solution containing 0.8 per cent. sodium chloride and 0.5 per cent. sodium citrate. When bleeding had entirely ceased the peritoneal cavity was carefully opened, without allowing any blood to escape into it, and was washed out with two or three changes of saline-citrate solution. A metal spatula was used to move the organs about in order to rinse them off, and the solution was drawn off mostly from the region of the liver and diaphragm, as this was thought to be the location in which young worms would most likely be found. An all-glass syringe without a needle was used for drawing off the fluid. The syringe was carefully washed with tap water before being used again for any other region.

The thoracic cavity was next opened and washed out in the same manner. The lungs and heart were then removed together and rinsed off, the apex of both ventricles was cut off and the trachea was clamped. The lungs were then irrigated by inserting a syringe filled with saline-citrate solution through the ring of the pulmonic valve of the heart, thus forcing the fluid into the pulmonary arteries. The blood-tinged fluid, returning through the left ventricle, was collected in a beaker. Irrigation of the lungs was continued until complete pulmonary edema was produced. By clamping the trachea, and thereby preventing the egress of air and fluid from the alveoli, the production of pulmonary edema was prevented until a satisfactory irrigation had been carried out. When the irrigation was finished the lungs were cut away from the main bronchi and were cut up into minute pieces with fine scissors. They were allowed to stand in saline-citrate solution for several hours before the final examination for young worms was made. This gave time for some of the worms, caught in the lung tissue or alveoli or still remaining in the blood vessels, to escape.

The liver was next removed after doubly clamping the portal vein at the hilus, to prevent young worms from escaping from either the liver or the mesenteric veins. After releasing the clamp on the liver side of the portal vein, the liver was irrigated by inserting the syringe into the various branches of the hepatic vein. The irrigating fluid escaped from the portal vein into a beaker. After thorough irrigation the liver was cut up into small pieces in saline-citrate solution, and after standing for several hours, the fluid was examined for young worms.

The next procedure was the irrigation of the mesenteric and splenic blood systems, and of the pelvic organs and posterior extremities together. In each case the irrigation was performed from artery to vein. In order to avoid contamination of the irrigating fluid a cannula was introduced into each artery and vein (except the splenic veins which were numerous), and the cannula from the vein was led directly into a beaker. A rubber tube connected the artery cannula with the irrigating syringe. None of these last three irrigations was easily performed, and occasionally the leg and mesenteric irrigations were not satisfactory, due, in the case of the legs, to escape of the fluid through an excessive collateral circulation, and in the case of the mesenteric circulation, to edema of the intestines, which was produced by the slightest obstruction to the venous outflow. Nevertheless, we believe these irrigations gave sufficient evidence to warrant our presentation of their results. The fluid from each irrigation, including the peritoneal and pleural washings and the lung and liver irrigations, as well as the

fluid containing the carotid blood, was allowed to stand in its beaker for a period of fifteen to thirty minutes, depending on the amount of blood in it, and was then carefully decanted, leaving one half to one inch of fluid in the beaker. The beaker was then refilled with saline-citrate solution and the decantation repeated until the fluid was water-clear. The sediment then remaining in the beaker was examined for young worms under a binocular dissecting microscope.

The popliteal lymph nodes, being the largest associated with the posterior extremity in the rabbit, were removed, placed in a little saline-citrate solution, and cut into minute pieces. After standing for several hours the fluid was examined for young worms.

The young worms from each locality were carefully counted, and their developmental stage estimated, using the arbitrary classification by Greek letters which we adopted in a previous paper of this series (II., pp. 56 to 75). Where a very large number of worms was found in any one locality, the stage of development was determined on a number large enough to establish the limits and average stage of development.

Observations of the gross pathological lesions in each of these rabbits were also made, paying particular attention to petechial hemorrhages.

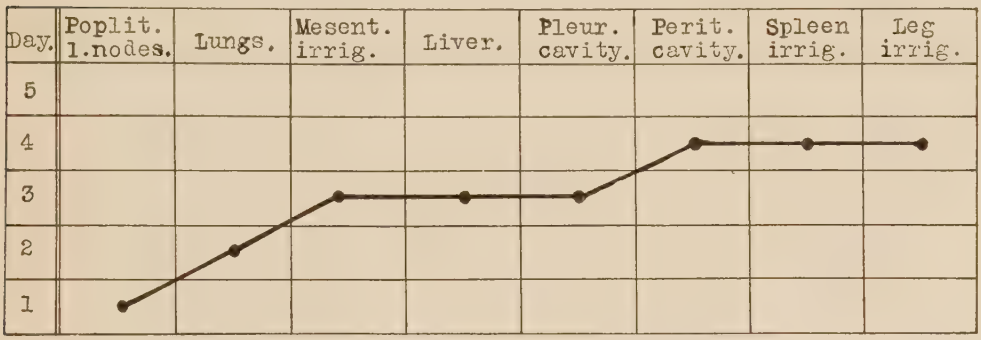
In order to corroborate the results of these experiments a similar series was performed on adult black-and-white mice. This series extended over a period of thirteen days, and was supplemented by the findings in other experiments in which the mice were killed at intervals up to thirty-one days after infection. Several groups of mice were used, each group being immersed together in a beaker containing heavily infected water. The same general technic was carried out as in the rabbits, except that the splenic, mesenteric and leg irrigations were impossible, and the inguinal lymph nodes were used instead of the popliteal.

One additional series of four mice was killed on the fourth, fifth, sixth and seventh days after infection. In this experiment, after washing out the peritoneal and pleural cavities and examining the washings for young worms, the lungs, diaphragm and liver of each mouse were fixed in ten per cent. formalin solution. The whole diaphragm, the upper lobe of the left lung and the largest lobe of the liver were imbedded in paraffin, sectioned serially and stained with hematoxylin and eosin.

Serial sections were also made of a portion of the stomach and a portion of one kidney of a rabbit killed four days after infection.

Results of experiments.

1. *Rabbit series.*—Table 1 gives a summary of the results of the rabbit experiments.* The first point which we wish to emphasize is brought out more clearly by Textfig. 1, which shows graphically the day on which the worms first appeared in the various localities. It will be noted that the worms were present in the mesenteric vessels and liver on the day after they first appeared in the lungs, on the same day on which they appeared in the pleural cavity, and on the day before they were first found in the peritoneal cavity. It will be seen from Table 1 that on the day on which they were first found in the liver they were already more numerous there than in any other locality except the lungs. These points make it seem unlikely that the worms reached the liver by way of the pleural and peritoneal cavities.



Textfig. 1. *Rabbit series.* First day on which young worms were found in various localities.

The second important point brought out in Table 1 is the fact that the worms disappeared from the lungs very rapidly after the third day. Less than one fifth as many were present in the lungs on the fourth day, as on the third. Since the worms arrived in the lungs by way of the blood vessels they must have been uniformly distributed throughout the parenchyma. It would be unreasonable, therefore, to suppose that four-fifths of the worms could have escaped from the lungs into the pleural cavity in one day. Furthermore, if they had passed into the pleural cavity we should have recovered more than we did from that location on the fourth day. A second possible avenue of escape from the blood vessels is into the alveoli of the lungs. In this case, they

* The preliminary experiments in this series were performed with the aid of Dr. B. C. Hou, of the department of pathology, Shantung Christian University School of Medicine.

must either have remained in the alveoli and bronchi, or they must have passed out into the trachea. It is hardly reasonable to suppose that eighty per cent. of the worms could have reached the trachea within twenty-four hours without the aid of a profuse secretion from the lungs. Of this there was no clinical evidence. Had they, on the other hand, remained in the alveoli and bronchi, we would have recovered them when we cut the lungs into fine pieces, and they would appear in our results as having been found in the lungs on the fourth day. The logical inference is, therefore, that most of the worms left the lungs by way of the blood stream; for that is merely a continuation of the route by which they entered the lungs, and the most rapid route by which they could have escaped.

TABLE 1.

RABBIT SERIES.

Numerical distribution of young worms on various days after infection.

Day.	Poplit. l. nodes.	Lungs.	Mesent. vessels.	Liver.	Pleural cavity.	Perit. cavity.	Splenic vessels.	Leg vessels.
1	2	0	0	0	0	0	–*	0
2	4	3	0	0	0	0	–*	0
3	15	262	3	22	5	0	0	0
4	2	46	0	106	12	1	2	2
5	0	14	13	253	1§	4	0	0
6	0	23	0	97	10	0	1	0
7	–*	1	37	758	0	1†	9	0
8	–*	3 + 2†	8	2443	0	1	6	0
9	–*	25‡	1	1352	171	1	0	0
10	–*	4	11	3213	0	0	0	0

Note.—The carotid blood is not represented in this table, because no worms were found in it on any of the ten days.

Let us next consider the results of our examinations of the liver, as shown in Table 1. Not only were the worms present in that organ in considerable numbers as early as the third day, but, with the exception of the sixth and ninth days, were recovered from it in rapidly

* Not examined.

† Large worms, with black guts, like stages found in liver. Apparently had broken through liver parenchyma into hepatic veins and returned to lungs, or into peritoneal cavity.

‡ This rabbit presented a picture of chronic passive congestion of all the viscera, which had apparently delayed the passage of worms through the lungs.

§ Faulty technic.

increasing numbers on each succeeding day, until on the last day of the series over three thousand worms were found. There are two factors which may help to explain this apparent gradual increase of worms in the liver. In the first place, we have evidence from a later experiment, in which we examined the liver of a mouse in serial microscopic sections on the fourth day after infection, that, on that day, most of the young worms plug the smallest branches of the portal vein in the form of emboli. They have not yet attempted to creep out into the larger blood vessels on their way to the mesenteric veins where they live as adults. Since they plug completely such small blood vessels at this early stage, a greater irrigating force would be required to dislodge them, than if they were larger, or occupied larger vessels without completely plugging them. Furthermore, by cutting up the liver into fine pieces we would be less likely to recover them at this early stage than we would later on, when they are larger or occupy larger blood vessels. This alone would satisfactorily explain their apparent gradual increase in numbers in the liver.

The second factor which helps to explain why the young worms were recovered from the liver in gradually increasing numbers, is that some of them were delayed in reaching that organ. This is shown by the fact that, as we have previously stated, very young developmental stages of the worms are found in the livers of experimental animals, even as late as the eleventh day after infection (II., pp. 70 to 72). Since the worms begin to develop rapidly after their arrival in the portal system, the youngest forms must be the latest arrivals, and were probably delayed, either in their efforts to reach the blood stream from the skin, or in passing through the capillaries of the lungs or gastro-intestinal tract.

This delay of some of the worms in reaching the portal system might be advanced as evidence that the worms leave the lungs mainly by way of the pleural cavity, and reach the liver by direct penetration of the host's tissues. As an isolated point of evidence this fact favors equally the course by the blood stream and that by direct penetration of the tissues, and therefore must be considered only in conjunction with other available evidence.

The results of our irrigations of the mesenteric, splenic and peripheral (leg) blood vessels, are, as we have already stated, not complete enough to warrant definite conclusions. Nevertheless, the fact that the worms were recovered from the mesenteric and splenic vessels as early as the third and fourth days, respectively, indicates that some of the youngest worms, at least, passed through these blood vessels. It

is probable, also, that all the worms which we recovered from these two blood systems, even up to the tenth day, arrived there by way of the mesenteric and splenic arteries. But, since both the mesenteric and the splenic veins are tributaries of the portal, and since we do not know how early the worms begin to creep back from the liver into these tributaries of the portal vein, we cannot be sure that some of the worms which we recovered from these vessels had not been previously in the liver.

The irrigation of the blood vessels of the posterior extremities and pelvis (last column of Table 1) gave very meager results. We can only call attention to the fact that the only day on which we recovered worms from these vessels was the day after they had been most numerous in the lungs, and the day on which one would expect them to be most numerous in all the peripheral capillary beds, if they left the lungs by way of the blood stream.

The fact that we failed to recover any worms from the carotid blood, collected when the animals were decapitated, appears to us to have little significance in regard to the course taken by the worms from the lungs. The animals survived for only about one minute after the severing of the blood vessels. During that time it might easily be possible that no worms left the lungs, and, if they had done so, they might have entered other peripheral arteries than the carotids.

It will be noted that the first worms recovered from the peritoneal cavity were found there one day after the first worms appeared in the liver, and that there were already 106 worms in the liver when the first one was found in the peritoneal cavity. This fact in itself suggests that the worms which were recovered from the peritoneal cavity may have arrived there by breaking out from the liver parenchyma, as they did from the lungs into the pleural cavity. We feel sure that at least one of the worms found in the peritoneal cavity did this. The one recovered on the seventh day had developed to a stage to which only worms which have resided for several days in the portal system can advance. Since worms reaching the liver by way of the blood stream might be carried to branches of the portal vein, very close to the peritoneal surface of the liver, it is not unreasonable to suspect that others, or even all of the worms found in the peritoneal cavity may have come from the liver. We cannot, however, exclude the diaphragm or, indeed, any other part of the visceral or parietal peritoneum as a possible point of entry for these worms.

The rabbit killed on the ninth day after infection furnished some very interesting information. The viscera all presented the gross

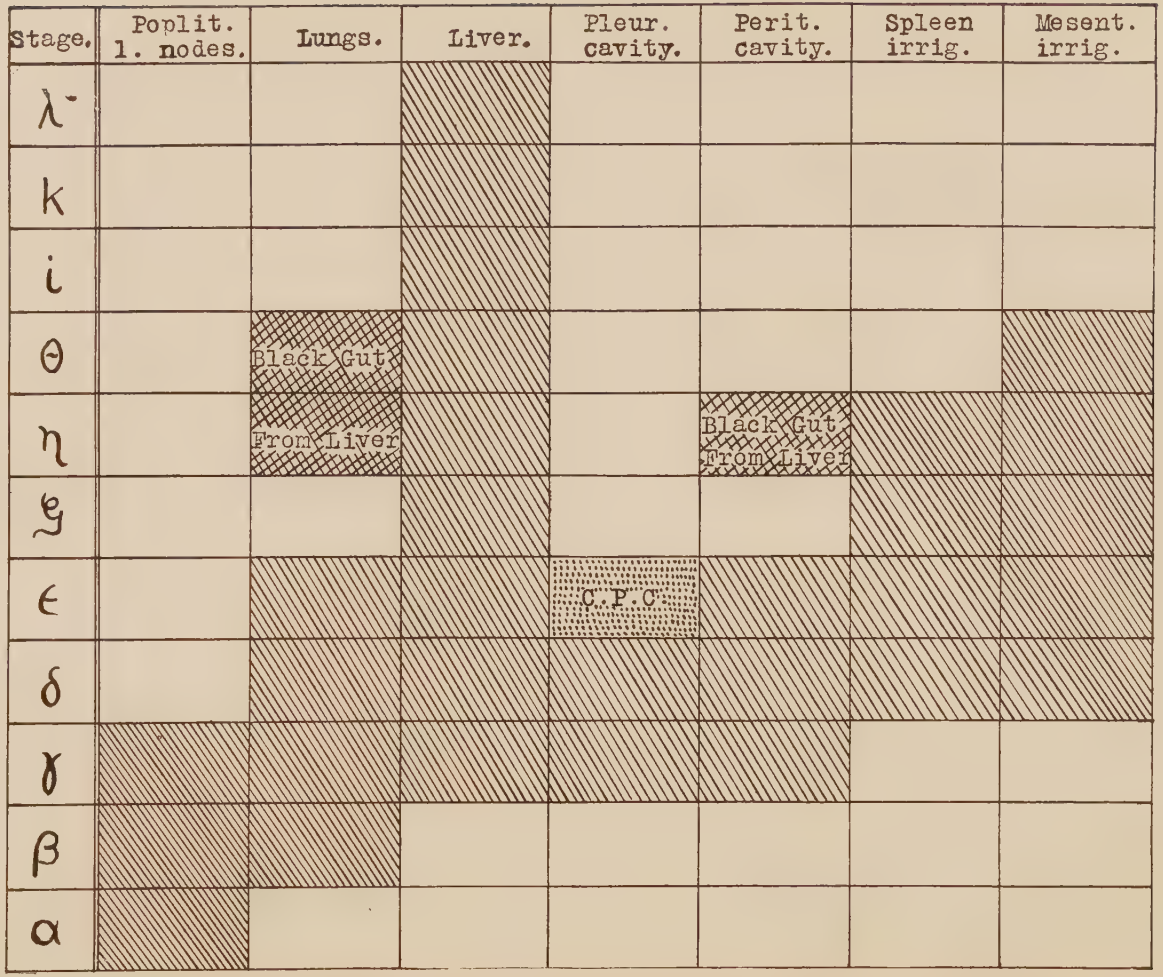
pathological picture of chronic passive congestion. There was considerable fluid in the peritoneal and pleural cavities, the spleen was slightly enlarged and was engorged with blood, the liver had a typical nutmeg appearance and the lungs were salmon in color. It will be seen from Table 1 that, although a large number of worms had reached the liver of this rabbit, still the lungs contained more worms than on any one of the preceding four days, and the pleural cavities contained the astonishing number of 171 young worms. From the peritoneal cavity, on the other hand, only one worm was recovered, even though there was about 100 c.c. of ascitic fluid in this cavity in which worms might have been suspended. This suggests that the worms had apparently been held in the lungs an unusually long time, allowing more than the ordinary number to escape into the pleural cavity. But with 171 worms, free in the cavities above the diaphragm, only one was found free in the cavity below it. This indicates that the diaphragm must act as a very effective barrier to the escape of the worms from the pleural cavity.

Textfigure 2 shows the developmental stages of the worms found in various localities in the rabbits. It will be seen that the "beta" stage is the youngest to appear in the lungs, and that the "gamma" stage is the first to appear in the pleural cavity, peritoneal cavity and liver. In other words the worms, after leaving the lungs, reach the liver at as early a developmental stage, as they reach any other locality.

This point not only coincides with the short period of time taken by the worms in reaching the liver, but it emphasizes the fact that some of the worms reach there, while they are still very small.

Textfigure 2 also shows that the worms are unable to develop in the lungs, pleural cavity or peritoneal cavity beyond the "epsilon" stage.* In the mesenteric and portal blood vessels, and perhaps in the splenic as well, they can grow to maturity. Now, if one considers the anatomical changes which take place in the young worms, another important point is brought out. We have previously shown (II., pp. 58 to 59) that the "gamma" stage of the worm is the most mature one in which the cephalic glands and their spine-tipped ducts are present. These glands are known to secrete a ferment, probably proteolytic in nature, and the spines are probably important instruments for the pene-

* Occasionally a worm escapes from the liver either through the capsule into the peritoneal cavity or through the parenchyma into the hepatic veins and thence into the lungs. These worms, being much larger and having a black gut, can easily be distinguished from worms which have not yet reached the portal and mesenteric veins. See Textfig. 2.



Textfig. 2. *Rabbit series.* Developmental stages of worms found in various localities.

Note.—Sections double-crossed represent young worms which had apparently passed from the liver into the lungs and peritoneal cavity. "C.P.C." represents a stage found in the pleural cavity only in the nine-day rabbit which showed chronic passive congestion of the viscera.

tration of the host's tissues. When these are gone, the only means of progression left to the young worm are the oral and ventral suckers and the power of contraction and extension. The backward pointing spines on the body of the worm may also keep it from moving backward. The worm is still admirably equipped for progress through a closed channel like a blood vessel, but has lost its main armament for penetrating solid tissue. Therefore, although the "delta" and "epsilon" stages of the worm were found in the lungs, pleural cavity and peritoneal cavity, it is possible that these forms are not able to pass out from those localities by direct penetration, and that unless they are carried away passively by the blood stream, they must die *in situ*.

2. *Mouse series.*—Table 2 and Textfigs. 3 and 4 show the results of the mouse experiments which parallel the rabbit series. The

TABLE 2.

MOUSE SERIES.

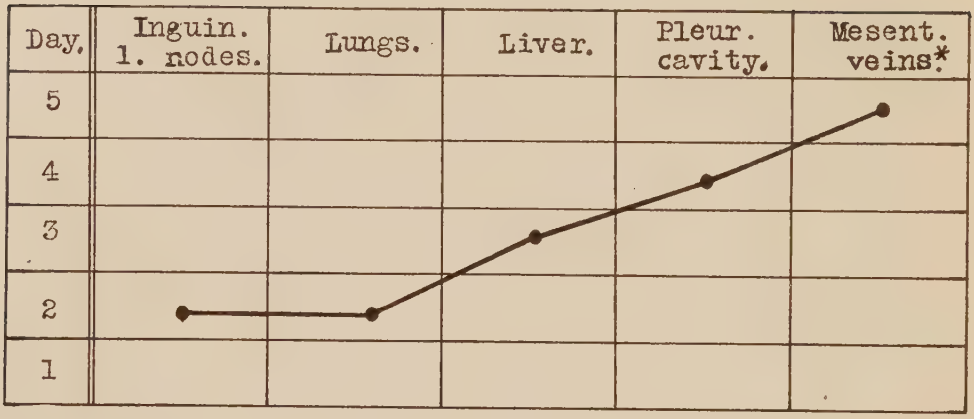
Numerical distribution of young worms on various days after infection.

Group.*	Day.	Inguin. l. nodes.	Lungs.	Liver.	Pleural cavity.	Periton. cavity.
a	1	0	0	0	0	0
a	2	10	13	0	0	0
a	3	10	75	1	0	0
a	4	0	61	15	9	0
b	5	1	3	139	25	0
b	6	0	34	134	8	0
c	7	–†	3	115	2	0
c	8	–†	4	28	2	0
c	9	–†	1	88	0	0
d	10	–†	3	109	0	0

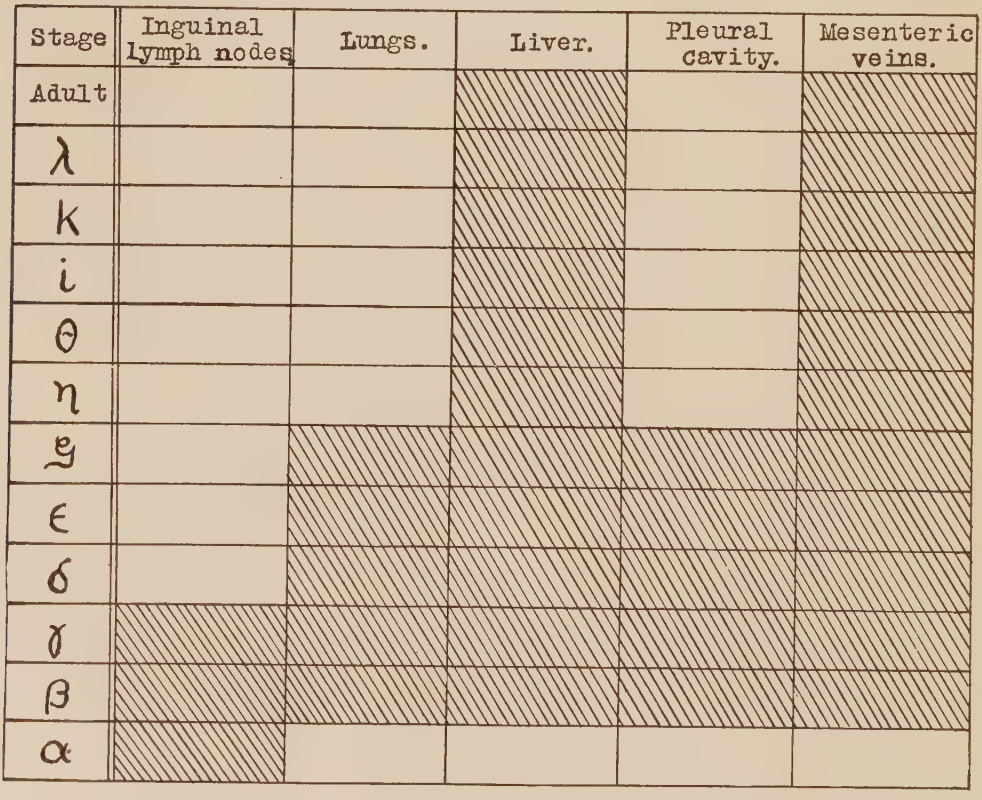
results are in general the same in the two series, but there are a few exceptions which deserve mention. First, it will be noted that no young worms were found free in the peritoneal cavity in any mouse (Table 2). Second, young worms were found in the liver one day earlier than they were found in the pleural cavity (Textfig. 3). Third, a stage of the worm, "beta," was found in the pleural cavity, mesenteric veins and liver (Textfig. 4), which was younger than any found in those localities in the rabbit. These differences may be accidental or may be due to differences in the size of the host. In either case, they

* Groups indicate mice immersed in same infected water at same time.

† Not examined.



TEXTFIG. 3. *Mouse series.* First day on which young worms were found in various localities.



TEXTFIG. 4. *Mouse series.* Developmental stages of worms found in various localities.

* Examined by teasing out the worms from the mesenteric veins.

emphasize the rapidity with which the worms reach the liver, and the improbability of their reaching that organ by way of the peritoneal cavity.

3. *Observations on hemorrhages in rabbits.*—Returning now to the rabbit series, we wish to call attention to the gross pathology, produced by this early period of the infection with *Schistosoma japonicum*. This is represented entirely by petechial hemorrhages, as far as we are concerned in these experiments. Table 3 shows the distribution of these hemorrhages on the various days after infection. It will be seen that,

TABLE 3.

RABBIT SERIES

Distribution of gross hemorrhages on various days after infection.

Day.	Poplit. l. nodes.	Lungs.	G. I. Tract.	Muscles, subcut. etc.	Liver.
1	±	+	0	0	0
2	0	+ +	0	0	0
3	+	+ +	+	0	0
4	+	+ + +	+ +	+ +	0
5	+	+ + +	+ + +	+ + +	0
6	0	+ +	+ +	+ +	0
7	–*	+	+ +	+	0
8	–*	+	+	0	0
9	–*	+†	+ +	0	C.P.C.†
10	–*	+	+	0	0

beginning with the popliteal lymph nodes, hemorrhages appear in practically all the tissues of the body, *with the exception of the liver, which is entirely spared.* The lungs are the organs which suffer most intensely and for the longest period of time (Fig. 1). This period extends beyond the duration of our rabbit experiments, but in a young dog which died thirty-three days after infection the lungs were entirely free from hemorrhages, although over ten thousand worms were recovered at autopsy from the portal and mesenteric veins. The gastro-intestinal tract, particularly the mucosa of the stomach, was the next region seen to be affected by hemorrhages. These began on the third day, and became very numerous on the fifth (Fig. 2), gradually fading thereafter, but persisting throughout the duration of the experiments. On the fourth day hemorrhages appeared in all the other parts of the

* Not examined.

† This rabbit showed the lesions of chronic passive congestion of the viscera.

body which were exposed, notably the deep layers of the skin, the striated muscles (including the diaphragm), the heart, and the kidneys. On the fifth day these were intense. The kidneys of the five-day rabbit are shown in Fig. 3. We counted 305 gross hemorrhages on the surface of these two kidneys. In these latter situations, however, the gross hemorrhages disappeared more quickly than from the gastro-intestinal tract, there being none visible after the seventh day.

Knowing that the hemorrhages in the lungs were caused by the presence of the young worms, we suspected that the hemorrhages in other localities were also caused by the presence of the worms. We therefore cut serial sections through a hemorrhage in the wall of the stomach, and through a portion of the cortex of the kidney of a rabbit killed four days after infection. In the stomach sections we found a worm lying free in the stroma of the mucosa, surrounded by a slight hemorrhage which had infiltrated between the gastric glands (Fig. 4). In the kidney sections we found young worms in the glomeruli, in tubules, and in the interstitial tissue, and in nearly every case the worm was close to a hemorrhage, which was usually into a glomerulus or adjacent convoluted tubules (Figs. 5, 6, 7).

It is noteworthy that the hemorrhages in the stomach were practically all in the mucosa, where the blood capillaries are most abundant, and were scarcely visible from the peritoneal surface of the organ. They were distributed with remarkable uniformity over all parts of the thin-walled fundus of the stomach, posteriorly, anteriorly and on both the greater and lesser curvatures. In the kidneys, the gross hemorrhages were also evenly distributed on all aspects of the surface, anterior and posterior, and in the microscopic sections the worms and hemorrhages were present, not only close to the surface, but to a less extent in the deeper parts of the cortex.

The occurrence of so many hemorrhages in the gastric mucosa raised the question whether they might be caused by direct penetration of young worms into the tissue from the stomach cavity. *Ascaris* and other nematodes reach the lungs by way of the blood stream and thence gain entrance to the intestine by way of the trachea, esophagus and stomach. It is therefore conceivable that the young schistosome might possibly take the same course, and reach the portal veins by penetration of the capillaries of the gastric mucosa. The fact that the cercaria of *Schistosoma japonicum* is quickly killed by 0.2 per cent. hydrochloric acid and by gastric juice, has been known for some time. This would not exclude the possibility, however, that a more advanced stage of the worm could live in such a medium. Ransom and Cram

(1921) state that Ascaris larvae, less than 800 micra in length, die in artificial gastric juice within three hours, while those over 1 mm. in length commonly survive. Therefore, in order to eliminate the possibility that young forms of *Schistosoma japonicum* could survive in the stomach long enough to penetrate the mucosa and enter the blood vessels, we performed the following experiment:

A rabbit was immersed for one hour in water containing the cercaria of *Schistosoma japonicum* from ten specimens of *Oncomelania*. Three days later the rabbit was killed and the young worms found in the lungs, pleural cavity and liver were placed in separate dishes containing 0.8 per cent. saline solution. They remained active and retained their normal outline and transparency. From this solution some specimens from each locality were placed in a solution containing 0.2 per cent. hydrochloric acid and 0.8 per cent. saline, and other specimens were placed in the filtrate from the stomach contents of the rabbit. In both these solutions the young worms ceased all motion within a period of three minutes or less, and became semi-opaque in consistency, as they do when fixed in formalin. Other specimens left in the 0.8 per cent. saline solution remained alive overnight in the refrigerator, and were active at room temperature the next day.

It is evident from this experiment that the gastric juice of the rabbit, as well as the degree of acidity normally found in the human stomach, are rapidly lethal to young specimens of *Schistosoma japonicum*, including not only specimens which are still in the lungs and pleural cavity, but also those which have already reached the liver. The possibility that the trachea, esophagus and stomach act as a path of migration of the worm from the lungs to the liver is, therefore, eliminated.

4. *Serial sections from infected mice.*—Our last series of experiments was one performed on four mice. They were killed on the fourth to the seventh day after infection, their pleural and peritoneal cavities were carefully irrigated, and serial microscopic sections were made of the whole diaphragm, of a lobe of one lung and of a lobe of the liver. Our purpose in this experiment was to determine whether many worms penetrated the diaphragm, and into what portion of the liver the worms first entered. The fourth day was chosen as the first on which to make these observations, since that was the first day on which young worms were found in the pleural cavity in the previous mouse series. Table 4 shows the results of these observations. It will be seen that worms were found in the pleural cavity on the fourth, fifth and sixth days, but not on the seventh. In the microscopic sections of the diaphragm one

young worm was found in the fat, adjacent to the diaphragm (not in a blood vessel), on the fourth day, none were found on the fifth and sixth days, and only two were found on the seventh day. Of these latter worms one was small, and was surrounded by mononuclear leucocytes (Fig. 8), the other was large and was surrounded only by a few red

TABLE 4.

MOUSE SERIES.

Numerical distribution of young worms in cavities and microscopic sections on various days after infection.

Day.	Lungs.	Pleur. cavity.	Diaphragm.	Perit. cavity.	Liver.
4	Many	4	1*	0	66
5	Fewer	11	0	0	–†
6	Few	11	0	0	58
7	Very Few	0	2	0	–†

blood cells (Fig. 9). Both were free in the tissues, and may, therefore, have arrived there, either by direct penetration from the pleural cavity, or by rupturing a blood vessel into which they had been carried by way of the arterial blood stream. It is evident that the younger of these two worms, being surrounded by a leucocytic reaction, still possessed the power of chemically injuring the host tissue, while the older worm had apparently lost this power.

The peritoneal cavity yielded no young worms in any of these four mice, which coincides with our former mouse series.

In the liver sections the young worms were carefully counted in the case of the four- and six-day mice. These gave such definite results that it was deemed unnecessary to go through the arduous work of a similar examination of the other two livers. It will be seen from Table 4 that, as early as the fourth day, a large number of worms had reached the liver; more, indeed, than would probably have been recovered from any other organ except the lungs. The important point, however, is that *every one of these young worms was in a blood vessel.* Of the sixty-six worms, fifty were demonstrated definitely to be in branches of the portal vein. (Figs. 10, 11, 12). These veins were identified by the presence of a bile duct, at one side of the vein. When the young worm completely plugged its blood vessel the adjacent bile duct was of course collapsed, but was definitely present and could often be found

* In fat, adjacent to diaphragm.

† Worms not counted.

more plainly in adjacent sections. Sixteen young worms were in blood vessels in which no duct could be demonstrated at one side of the vein (Fig. 13), although in most cases the position of the vessel in relation to other vessels indicated the probability that it was a portal vein rather than a central (efferent) vein. No worm was found in any vessel which was definitely an efferent vein. Neither were any worms found penetrating the surface of the liver or free in the parenchyma, or even in blood capillaries within a liver lobule. Another striking fact was the even distribution of the worms throughout the lobe of the liver. Just as many were found in the central portion, in proportion to the number of small blood vessels there, as in the peripheral portion of the lobe.

Another point of importance in connection with the position of these worms was the fact that, of the sixty-six worms, fifty-five completely plugged blood vessels, apparently acting as emboli (Figs. 12, 13). Usually the worms were stretched out in the vessels, but occasionally one was found bent double on itself.

It is a significant fact that there was no tissue reaction or hemorrhage about the worms in the liver, as there was in the diaphragm, lungs, stomach and kidneys. There was no apparent attempt of the worms in the liver to escape from the blood vessels, presumably because they were in the proper environment for development to maturity. If these worms had gained entrance to the blood vessels of the liver by active penetration of the liver substance from outside, not only would they have been most numerous near the peritoneal surface, but the liver tissue would have been torn, and there would have been hemorrhage and possibly a leucocytic reaction about the worms.

The liver of the six-day mouse corresponded accurately with that of the four-day mouse in microscopic findings. The only difference was in the larger size of the worms.

This experiment demonstrates, then, that the young worms arrive at the liver in large numbers on the same day on which they are first demonstrated in the pleural cavity; that they are evenly distributed throughout the liver; that, even on that day, they all occupy blood vessels, mostly portal veins; and that in gaining that position they produce no demonstrable lesion of the liver tissue. These facts alone, would lead one to assume that the worms reach the liver by way of the afferent blood stream.

Discussion.

We feel that these experiments permit of only one conclusion, namely, that the vast majority of the young forms of *Schistosoma*

japonicum leave the lungs by way of the pulmonary veins and are distributed diffusely throughout the host's body as emboli in the systemic capillaries. Because of the large size of the arteries leading to the spleen and gastro-intestinal tract, a large proportion of the worms are thrown into the capillaries of those organs. Those which are small enough stretch themselves through the capillaries without rupturing them, just as they did in the lungs. The stomach and intestines, being composed of soft and elastic tissues like the lungs, are well suited for such passage. The young worms are then thrown into the liver as emboli, where they lodge in the small portal veins, grow rapidly, and later migrate back toward the mesenteric veins. A few may rupture the blood vessels of the liver, and break through into the peritoneal cavity, or into an hepatic vein, whence they are carried as emboli to the lungs.

The young worms which are too large to work their way through the gastro-intestinal and splenic capillaries, break out into the tissues and cause a hemorrhage. Some of these worms probably gain entrance to blood vessels again and ultimately reach the liver, others probably die in the tissues of the organ in which they are arrested.

In the case of young worms lodging in other systemic capillaries, some work their way into the veins without rupturing the vessel, and then return to the lungs as emboli a second time. Others rupture the vessel, produce a hemorrhage, and either regain a vessel, or die in the tissue, or escape with the secretion of the organ in which they lie. This last condition may obtain in the kidney. We found young worms in the convoluted tubules of the kidney (Fig. 6), and it is conceivable that careful examination of the urine of a recently infected animal might reveal the presence of young worms excreted by the kidneys. We intend to make such examinations when the opportunity offers.

We believe that it is clear why Narabayashi and Sueyasu, on the one hand, and Miyagawa and Takemoto on the other, came to opposite conclusions as to the course taken by the young worms from the lungs to the liver, although they used the same methods in their experiments. The observations of all of these workers were undoubtedly accurate, but Narabayashi and Sueyasu drew their conclusions entirely from the location of the worms found, without sufficiently considering by what path the worms might have arrived where they were found, or whether they would be able to reach the liver from that location. A worm found in the diaphragm, for instance, may have arrived there either by way of the blood stream or by direct penetration from the pleural cavity. But, even if it had penetrated into the diaphragm from the

pleural cavity, its presence there would be no indication that it could continue to penetrate until it found its way into a portal vein in the liver. There is a gradual development of the young worms in other places than the liver as far as the "epsilon" stage, but after they have passed the "gamma" stage they lose an important part of their armament for the direct penetration of the host's tissues. Even if such penetration is possible for the older forms, their progress must be very slow, and death probably occurs before most of the young worms which are free in the tissues can reach the portal veins.

It should be stated in fairness to Narabayashi and Sueyasu, that they both granted the probability that some worms left the lungs by way of the pulmonary veins and were carried to the systemic capillaries by the arterial blood stream. Narabayashi (1916) shows photomicrographs of young worms in an artery of the kidney and in the placenta, both of which locations could have been reached only by way of the aorta. Sueyasu (1920) also states definitely that the arterial blood stream is a secondary path by which the worms reach the liver.

Summary and conclusions.

1. It is well established that the cercariae of *Schistosoma japonicum* enter the mammalian host primarily through the skin, that they gain access to the lymph and blood vessels, and that they reach the lungs by way of the great veins, the heart and the pulmonary arteries.

2. Narabayashi, and later Sueyasu, by examining serial microscopic sections of mice, recently infected by *Schistosoma japonicum* concluded that the young worms left the lungs mainly by way of the pleural cavity, worked their way through the mediastinal tissues (Narabayashi) or the diaphragm (Sueyasu), and thence penetrated the liver and the portal and mesenteric veins.

3. Still later Miyagawa, using similar methods, concluded that the principal course taken by the young worms from the lungs was through the pulmonary veins to the heart and arterial circulation, whence some passed through the capillaries of the gastro-intestinal tract into the mesenteric and portal veins, where they grew into adult forms.

4. We attacked this problem by somewhat different methods. A series of ten rabbits was heavily infected, and one animal was killed each day for the first ten days after infection. The peritoneal and pleural cavities were washed out, and the blood vessels of the lungs, liver, spleen, gastro-intestinal tract and posterior extremities were irrigated with saline-citrate solution. The popliteal lymph nodes,

lungs and liver were also cut into fine pieces, washed and the fluid examined for worms.

5. The young worms were first recovered from the liver on the same day on which they were first found in the pleural cavity and on the day before they were first found in the peritoneal cavity. They could be found in the pleural and peritoneal cavities only in small numbers, except when there was a condition of chronic passive congestion of the viscera. In this case they were present in the pleural cavity in large numbers, but in the peritoneal cavity in very small numbers.

6. A similar series of mouse experiments yielded essentially similar results.

7. In the rabbits, observations were also made on the distribution of petechial hemorrhages, on various days after infection. Serial sections through a petechial hemorrhage in the stomach and through the kidney cortex of a four-day rabbit revealed young worms surrounded by hemorrhage in both these localities.

8. Young worms recovered from a rabbit, three days after infection quickly died in the rabbit's gastric juice and in 0.2 per cent. hydrochloric acid, thus eliminating the possibility that the worms leave the lungs by way of the trachea, pass down the esophagus into the stomach and enter the portal blood vessels by penetrating the gastric mucosa.

9. In a second series of mice, killed on the fourth to seventh day after infection, the diaphragm and one lobe each of the liver and a lung were sectioned serially. The pleural and peritoneal cavities were washed out and the washings examined for young worms. The pleural cavity yielded a few worms, the peritoneal cavity none. The lungs contained many worms on the fourth day, but decreasing numbers thereafter. The diaphragm sections revealed one worm on the fourth day, none on the fifth and sixth, and two on the seventh. The serial sections of the liver showed sixty-six worms on the fourth day. They were distributed evenly throughout the liver, and every one was in a blood vessel, fifty being definitely in portal veins. Fifty-five completely plugged vessels, suggesting that they were acting as emboli. There was no tissue reaction or other indication of penetration of the worms into the liver tissue from the peritoneal surface.

10. We conclude from these observations that the main course taken by the young forms of *Schistosoma japonicum* from the lungs to the liver is by way of the pulmonary veins, the arterial circulation, the gastro-intestinal capillaries and the mesenteric and portal veins.

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EXPLANATION OF PLATES XIII to XV.

ABBREVIATIONS.

P.—Young *Schistosoma japonicum.*
H.—Hemorrhage.
D.—Bile duct.

FIG. 1. Lungs of rabbit, five days after infection by *Schistosoma japonicum.* Posterior view.

FIG. 2. Inner surface of stomach of rabbit, five days after infection. A coating of mucus hides the hemorrhages in the region of the lesser curvature.

FIG. 3. Kidneys of rabbit, five days after infection.

FIG. 4. Young *Schistosoma japonicum* in mucosa of stomach of rabbit, 4 days after infection. Note hemorrhage in tissues near worm. × 200.

FIG. 5. Young worms in two glomeruli of kidney of rabbit, four days after infection. × 100.

FIG. 6. Young worm in convoluted tubule of kidney of rabbit, four days after infection. Note hemorrhage in adjacent tubules.

FIG. 7. Young worm in kidney of rabbit, four days after infection. The space about the worm may have been occupied by a glomerulus. × 100.

FIG. 8. Young worm, surrounded by cellular infiltration, in diaphragm of mouse, seven days after infection. × 200.

FIG. 9. Another worm in diaphragm of mouse, seven days after infection. The worm is larger than that in figure 8, and there is no cellular infiltration about it. × 200.

FIG. 10. Young worm in large branch of the portal vein of a mouse, four days after infection. × 100.

FIG. 11. Young worm in a small branch of the portal vein of a mouse, four days after infection. × 200.

FIG. 12. Larger worm completely plugging a small branch of the portal vein of a mouse, six days after infection. × 200.

FIG. 13. Worm completely plugging a small vein which cannot be positively identified as a portal vein, because no bile duct can be made out. × 200.

Fig. 1

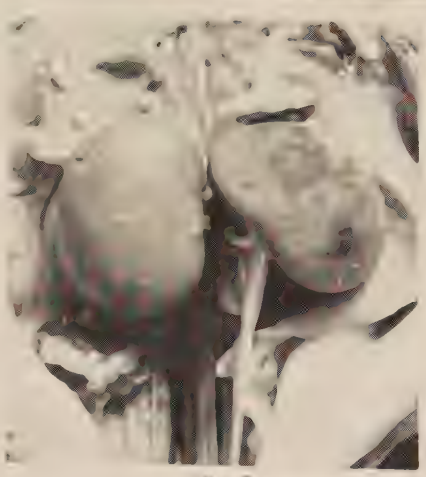


Fig. 3

Fig. 2

(Faust and Meleney: Studies on Schistosomiasis Japonica, III.)

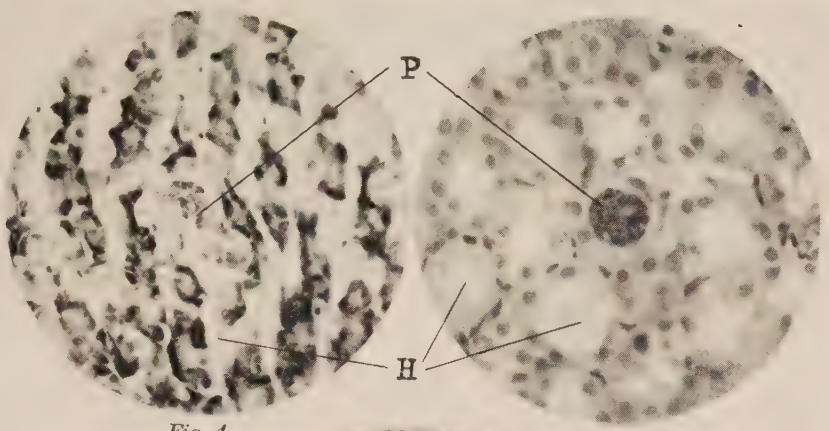


Fig. 4

Fig. 6

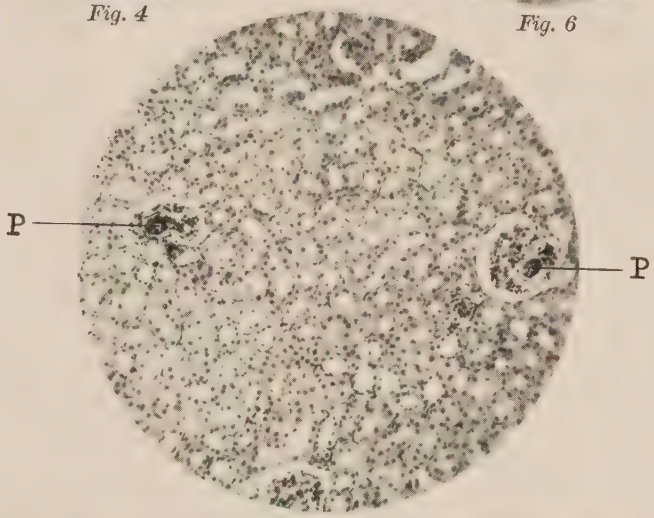


Fig. 5

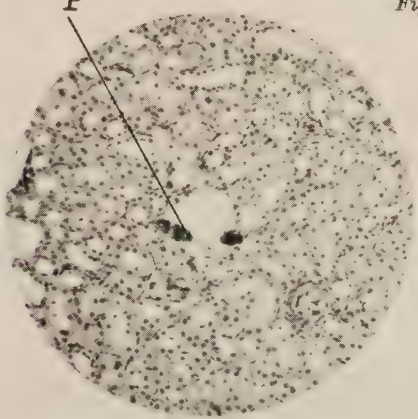


Fig. 7

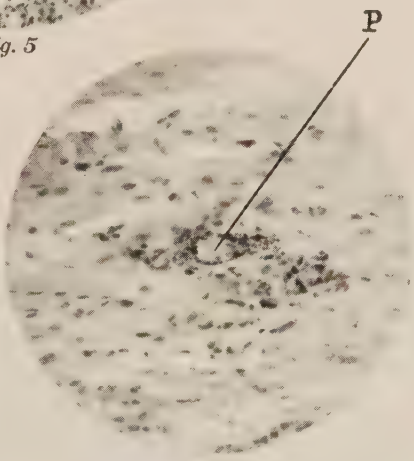


Fig. 8

(Faust and Meleney: Studies on Schistosomiasis Japonica, III.)

Fig. 9

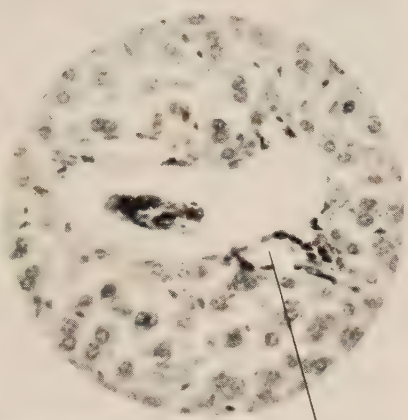


Fig. 11

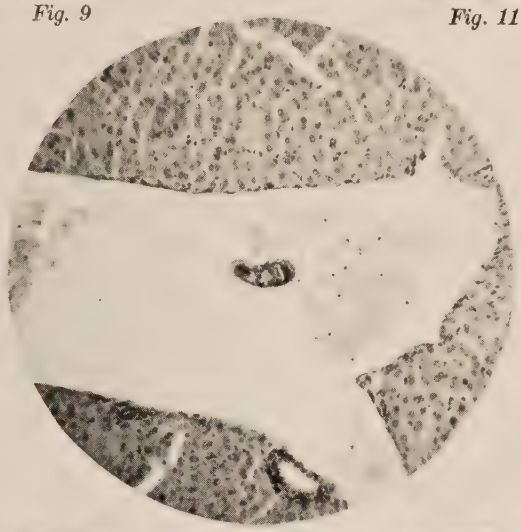


Fig. 10

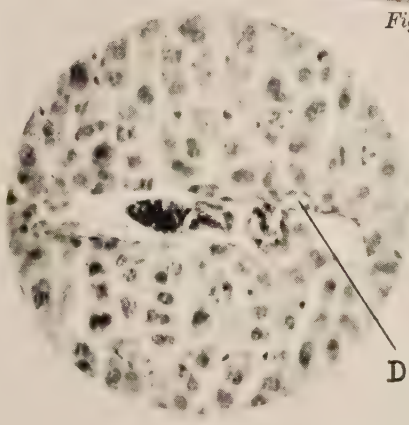


Fig. 12

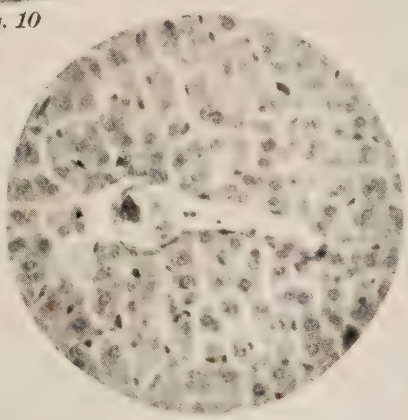


Fig. 13

(Faust and Meleney: Studies on Schistosomiasis Japonica, III.)

IV. THE INTERMEDIATE HOSTS OF *SCHISTOSOMA JAPONICUM* AND THEIR KNOWN RELATION TO SCHISTOSOMIASIS JAPONICA IN THE ORIENT.

(Plates XVI to XXI.)

Introductory.

One of the first facts which faced us in our study of schistosomiasis japonica was that the mollusc which acts as the intermediate host for *Schistosoma japonicum* in China had never been recognized. General statements had been made to the effect that it probably was the same snail, *Katayama nosophora* Robson, 1914, which acts as the intermediate host in Japan. But this snail, if it had ever been found in China, had as far as we know, never been examined for the cercaria of *Schistosoma japonicum*. Realizing that any attack upon the disease in China would first of all demand the recognition of its intermediate host, we determined to search for the host in an endemic area.

Historical.

In the early months of 1913 Miyairi and Suzuki (1914) discovered that the snail now known as *Katayama nosophora* (Syn. *Blanfordia nosophora* or *Hypsobia nosophora*) was the intermediate host for *Schistosoma japonicum* in the endemic area of the disease on the island of Kyushu, Japan. Leiper and Atkinson (1915), unaware of this discovery, came to China from England early in 1914 for the purpose of finding the intermediate host of the parasite involved in this disease. Their work was intended to be preliminary to the solution of the same problem in connection with the human schistosome diseases of North Africa, where the necessity of a molluscan intermediate host for these parasites had been disputed by Looss for many years. Leiper and Atkinson searched in many places along the Yangtze Valley, but failed to find a snail which contained the form of cercaria, described by Miyagawa (1913) as that of *Schistosoma japonicum*. Failing in China, Leiper and Atkinson went to Japan, where they first heard of the work of Miyairi and Suzuki. They visited the Katayama endemic area, where the worm had first been discovered by Katsurada in 1904, and their observations and experiments corroborated those of Miyairi and Suzuki, and cleared up some of the steps in the development of the worm in the snail. They found the same snail to be the intermediate host in Katayama as on

Kyushu. It has since been established that some member of the genus *Katayama* is the host of the worm in all of the five endemic areas of Japan. Leiper and Atkinson returned to China from Japan, and spent the early part of the summer of 1914 in the lower Yangtze Valley, including the region about Soochow, but failed to find either *Katayama nosophora* or any other snail which contained the cercaria of *Schistosoma japonicum*. Their search might have ended successfully, had it not been cut short by the outbreak of the Great War.

So far as we are aware, no systematic search for this intermediate host has been made since that time. Annandale (1918) made a survey of the molluscs of one small area of the Tai Hu (or Great Lake), and of some of the canals of Soochow. He found *at the bottom* of the Tai Hu, at a depth of about nine feet, a snail averaging three millimeters in length, which he says he could not differentiate (except in size) from Heude's *Hypsobia humida*, and which he named *Hypsobia minuscula*. He says nothing about its infection by *Schistosoma japonicum*, although he knew that *Katayama nosophora*, which he at that time regarded as a Hypsobia was its host in Japan.

Biological and practical aspects of the problem.

It is a fact of extraordinary biological significance and practical importance that *Schistosoma japonicum* has become adapted to the intermediate molluscan hosts which it utilizes. The amphibious habits of this group of snails, the local conditions under which they live, and their ability to withstand long periods of desiccation, have not only caused the adjustment which the schistosome parasite has made to them to be very intimate, but have made the bionomic and preventive phases of the problem of schistosomiasis japonica peculiar unto themselves.

On the purely biological side of this question we have had to consider not only the chemotactic aspect of the adjustment, but also the mechanism whereby the miracidium finds the proper snail host and effects entry into it. We have shown in a preceeding section of this paper (II, pp. 29 to 33) that the miracidia of *S. japonicum* collect in the top two or three centimeters of the water in which they hatch, and that this is the optimum location for attacking the molluscan host to which they are adjusted, inasmuch as these snails collect in or above the surface film soon after they are placed in a given body of water. More recent field work on our part has shown that in nature the snails involved are invariably found in or on loose moist soil or on moist vegetable matter, above the apparent level of the water,

although in fact they are really in the water film, since the capillary properties of the soil tend to raise the water level of the ground above the main source of water supply. One of us (E.C.F.) has had an opportunity of making a comparative study of the relation of the miracidium of *Schistosoma haematobium* to the molluscan host, *Bullinus contortus*, at Cairo, Egypt, which observations have a definite bearing on the specific adjustments of these two related human blood flukes and the molluscan hosts which they infect.

Eggs of *Schistosoma haematobium* from urine of an infected patient were centrifuged slowly for two minutes and then washed several times in luke-warm tap-water. They were then placed in a cylinder glass and allowed to hatch. Observations were made on the number of miracidia collecting at various levels of the water. Several counts from several samples of material demonstrated that there was an equal distribution of the miracidia throughout the medium. Specimens of *Bullinus contortus* were then placed in the bottom of these containers and the reactions of the miracidia studied. The miracidia attacked the latter almost immediately at all levels of the water column, and two hours later had all disappeared from the water.

These observations indicate that the behavior of the two species of miracidia differs in this respect, that the larvae of *S. japonicum* collect very soon after hatching near the top of the water column and are in a position to infect only those snails found in this stratum. On the other hand, the larvae of *S. haematobium* are quite equally distributed throughout the water and are in a position to attack at any level the snail to which they are adjusted. It seems probable, therefore, that the specialized adaptation of the miracidia of *S. japonicum* for the amphibious operculate snails which they select and invade, precludes them from utilizing unrelated operculate or non-operculate snails as hosts, even if the chemotactic phenomena of the miracidia for these several groups of snails were the same. This has an important bearing on the practical phases of the problem in the field. It was with this knowledge of the unique reaction of the miracidia of *S. japonicum* in seeking the upper water stratum soon after hatching, and their adaptation to the Japanese snail, *Katayama nosophora*, that we set out on the search for the intermediate host of the parasite in China.

Method of procedure.

We had previously observed that miracidia of *Schistosoma japonicum*, hatched from the ova contained in feces from a Chinese patient from the Yangtze Valley, would successfully develop to the secondary

sporocyst stage in *Katayama nosophora* from Japan. We, therefore, surmised that the Chinese host was probably a snail of similar habits and chemical reactions to the Japanese host. We had had an opportunity, also, to study the habits of the Japanese host in the laboratory, and one of us (H. E. M.) had visited the Katayama endemic area in Japan and had observed the snail in the rice fields and irrigation ditches of that region. We therefore decided to visit certain endemic areas somewhere along the Yangtze Valley, to determine from hospital records the exact locality from which cases of schistosomiasis had come, to attempt to find cases of the disease in such a locality, and to look for a snail similar to the Japanese host in the neighborhood. If such a snail was found, and on examination contained cercariae morphologically similar to that of *Schistosoma japonicum*, the procedure would then be: first, to immerse mice, brought up in confinement, in water containing these cercariae, and, after a suitable time, examine them for adult schistosomes; and second, to observe the reaction of miracidia of *Schistosoma japonicum* to these snails, and if possible to infect snails with miracidia. This infection could be proved, first by making serial sections of snails at various intervals after exposure, in order to follow the metamorphosis and metagenesis of the miracidia in the snail; and second by obtaining mature cercariae from the snails at the proper interval after exposure.

Endemic areas surveyed in China.

Our search for the molluscan hosts of *Schistosoma japonicum* has been confined to three areas in Central Eastern China, where the disease caused by the parasite was known to be a serious menace to the country, and to one area in South China, where there was suspicion of the existence of the infection. For convenience these four investigations will be treated under separate headings. The first search for the snail involved in the infection, that in the Soochow area, was conducted by Doctor Meleney. The other three surveys were carried on by Doctor Faust. These are supplemented by a study of the groups of snails involved in schistosomiasis japonica in the Far East, which Doctor Nelson Annandale, Director of the Zoological Survey of India, has kindly written for us. (See appendix A.)

A. The discovery of the molluscan intermediate host of *Schistosoma japonicum* in the Soochow area.

(Plates XVI to XVIII.)

The endemic area about Soochow, Kiangsu Province, was selected

for our first search. This region was known to be heavily infected with schistosomiasis, and the new Soochow Hospital under Dr. John A. Snell afforded facilities and cooperation for conducting the investigation.

Soochow, known as the "Venice of China," contains within its walls a network of canals, and the surrounding country is also finely interlaced with water channels. There are, in addition, many lakes in the vicinity, including China's greatest lake, the Tai Hu. These lakes furnish the water for all the canals of the region. The largest of these canals, including the Grand Canal, act mainly as thoroughfares for boat traffic. Smaller secondary canals, sometimes many miles in length, run off from these at right angles; and these, in turn, have still smaller tertiary branches, which either end blindly or connect with other secondary canals. From any of these three classes of canals there may be small terminal branches leading out into cultivated regions. These terminal branches are used mainly for irrigating purposes.

Irrigation is accomplished usually by means of tread wheels (Figs. 1 and 2), turned either by water buffalo or oxen or by human foot power, which lift the water from the canals into the rice fields. The water in the canals, coming, as it does, from lakes, is relatively clear. It is frequently renewed because of its use on the rice fields, and therefore does not become stagnant. The presence of fish, frogs, snails and other life in the canals also aids in keeping the water clear. The rice fields are from four to six feet above the level of the canals. This condition is in contrast with that close to the Yangtze River, where the river itself supplies the canals with water, and where the rice fields are below the level of the canals. In the Soochow district, therefore, the rice fields are relatively dry except in very wet weather, and mechanical effort is necessary to keep them in condition for the growing of rice. In the winter months, when they are not planted to rice, they remain quite dry, and are used for a winter crop of wheat.

The villages in this district consist of small groups of houses, either along both sides of a canal or about the end of a terminal canal. The houses are built of mud and plaster, with tile or thatched roofs. In the larger villages the canals are faced in by perpendicular stone walls, and the houses often abut directly on these walls with a flight of stone steps leading down to the water. In smaller villages the nearest houses are usually from ten to twenty feet away from the canal and from four to six feet above it. Practically all the houses are in close proximity to a canal.

Most of the people, both adults and children, go barefooted. If any footwear is worn, it is merely a straw sandal. They go freely

into the water, while repairing their boats and washing vegetables. The boys and young men also swim in the canals. No suspicion of any connection between the canal water and any disease exists among the people.

Human fecal material is used for fertilizer. It is therefore deposited in large "*k'angs*" or earthenware tubs near the houses, and is stored in these vessels or in holes in the ground until the season of the year when the fields are fertilized. This method of disposal of fecal material doubtless prevents most of the ova from infected persons from hatching before the embryos die. However, as there are paths through the rice fields and along the canals, children or persons suffering from diarrhea may defecate close to or into the water and thus afford the schistosome embryos a proper medium for hatching and for seeking an intermediate host.

The domestic animals of these villages include water buffalos, oxen, dogs, cats, chickens, ducks and geese. No wild mammals were observed, and field mice have not been noted by the inhabitants of the region. A few water rats have been seen about the larger canals.

Identification of the host.

We went by motor boat into a region north of Soochow where cases of schistosomiasis were known to have occurred (Fig. 3). This region, which is north of the town of Loh'Mm, is known as Hsü Chwang (Village of the Hsü family). After leaving our boat we visited several groups of houses without seeing any clinically positive cases of schistosomiasis. We searched for snails in the rice fields, which were either so dry that the soil was caked and deeply cracked open, or were just being watered. A few snails belonging to the genera *Lymnaea* and *Bythinia* were found in an irrigation ditch, but only the shells of dead snails were found in the rice fields. After two hours' search, however, an advanced case of the disease, with marked ascites, was encountered (Fig. 4), and fecal specimens from three persons living in a small group of houses near at hand were found to contain ova of *Schistosoma japonicum*. These houses were found to be at the side of a small terminal canal (Fig. 5). On the shore of this canal, just above the water's edge, were found hundreds of small snails, quite similar in appearance to *Katayama nosophora*, except for details which will be described later.

On returning to the laboratory these snails were crushed in watch glasses, either singly or in groups of ten, and in seven out of two hundred and forty snails crushed, we found fork-tailed cercariae which in size, shape and activity corresponded exactly to the cercaria of *Schistosoma japonicum* (Fig. 6). Specimens were fixed in formalin, stained,

and found to correspond also in internal anatomy. Besides these cercariae, one snail contained about a dozen fork-tailed cercariae of a different type (having two pigment eye spots), and another (snail) contained many straight-tailed cercariae.

The watch glasses containing the first type of fork-tailed cercaria were washed into a small museum jar, and two young white mice which had been bought in the market in Soochow and which had never been in contact with water that could have contained schistosome cercariae were immersed for one hour in this water. Fourteen days later one of these mice was sacrificed, although still apparently well, and from the liver and mesenteric veins were obtained about one hundred young schistosomes. Thirty-one days after immersion, the other mouse was sacrificed, and 171 adult schistosomes, morphologically similar to the Japanese variety, were recovered from the liver and mesenteric veins. Of these worms, twenty-nine pairs were in copula (Fig. 7).

Three days after the first collection was made many more similar snails were collected in the same locality, and were placed in a cylinder containing water in which many miracidia of *Schistosoma japonicum* were present. The ova from which these miracidia had escaped were obtained from the feces of a patient with clinical schistosomiasis. The snails, following their usual habit, climbed rapidly up the sides of the cylinder. As they approached the surface of the water, they were observed with a hand lens, and miracidia were seen to become attached in large numbers to various parts of the body surface, and to remain there until the snail was entirely out of the water. These snails were then set aside in sterilized, filtered canal water. Water grass, sterilized in 0.5 per cent. potassium permanganate solution, was added to the water to provide nourishment. The snails were killed in hot 10 per cent. formalin, at intervals of five to eleven days.

Serial sections of these and other similarly treated snails have shown the development of the miracidia into mature cercariae within the snail (Figs. 8, 9, 10, 11).

Similar snails were later found in a canal within the city of Soochow, but no cercariae of *Schistosoma japonicum* were found in the 400 which were examined. Therefore, a group of these snails was exposed to miracidia. They were then kept in water under the best possible conditions, adding water grass and occasionally soil from the bank of a canal. On the seventy-second day after exposure, one of these snails was killed in hot 10 per cent. formalin, imbedded in paraffin and cut in serial section. Mature and maturing cercariae of *Schistosoma japoni-*

cum were found in the region of the snail's liver. On the eighty-sixth day after exposure, the surviving snails of this group, twenty-six in number, were crushed. Ten were found to be infected, eight with immature sporocysts, two with mature cercariae of *Schistosoma japonicum*. A white mouse was immersed for one hour in water containing these cercariae. Seventy days later this mouse died and was found to harbor six male and five female adult specimens of *Schistosoma japonicum*. In this way the life cycle of the *Schistosoma japonicum* from Soochow was completed in the laboratory, from ovum to adult.

The molluscan host.

The mollusc from which the cercariae of *Schistosoma japonicum* were obtained is a small operculate gasteropod, with an acuminate shell measuring from 4.2 to 9 millimeters in length and from 2.1 to 3.8 millimeters in breadth. The coil of the shell is dextral and consists of seven spirals. The terminal spiral is often eroded. The lip of the shell aperture sometimes ends in a thin flaring edge, while sometimes there is a prominent terminal "varix," with constricted edge. The shell is semi-opaque, is sometimes uniformly dark brown in color, sometimes partly brown and partly straw-colored, sometimes entirely straw-colored. It is moderately hard, requiring considerable force to crush it. The shell is usually clean, but, in relatively still water, is sometimes discolored green with algal growth or white with lime incrustations. The shell is not smooth like that of *Katayama nosophora*, but is traversed at regular intervals by prominent "costules" at right angles to the spiral groove of the shell, and therefore parallel to the lip of the shell aperture. The operculum is egg shaped, with eccentric nucleus and with subspiral lines curving outward from the nucleus convexly to the right. Mr. Bryant Walker of Detroit, Michigan, has kindly examined the snail for us and has identified it as *Oncomelania hupensis** Gredler (Fig. 12).

The habits of this snail are quite different from those of any other snail found in the same region. In warm weather it inhabits the moist earth, just above the water's edge, always within 50 cm. of the water and usually within 10 cm. of it. It is found attached to the earth, to stones or to the stems of grass or plants growing out of the water. It

* Heude (1890) made extensive researches on the molluscs of the Yangtze Valley. Owing mainly to the difference in habitat between *Melania* and the genus which Gredler had called *Oncomelania*, Heude renamed the latter *Hemibia* and divided the genus into many species. His *Hemibia Schmackeri* (Möllendorf) was found nearer to Soochow than any other form described by him, that snail having come from the Great Lake (Tai Hu) a few miles south-west of Soochow.

prefers sloping banks but avoids exposure to the sun (Fig. 13). It must therefore be searched for in secluded spots, beneath loose grass, under projecting clods of earth or beneath stones. The bodies of water on whose shores it is found are relatively clear, cool and still. It has not been found in large canals where there is much traffic and where there is, therefore, much movement of the water, but may be found not over four or five meters from such a canal, in a small terminal branch. It may be found singly or in groups. A hundred or more may be picked up without moving one's position, or, on the other hand, careful search in a similar spot may reveal only a few, or even none. It is occasionally found on stones or roots of grass, a few centimeters below the surface of the water, but dredgings of deep water-grass have not been found to contain it, nor has it been found in the bottom of a canal on whose shore it was abundant.

In the laboratory, if placed in a deep glass dish in shallow water, it usually climbs out from the water in a few minutes, on the side of the dish away from the window, and, after creeping far enough to free itself from water, will fasten its shell to the glass by mucus at the aperture, retreat into its shell, and remain there for hours or days. It may drop or creep back into the water, or may possibly remain desiccated until death. Reimmersion in water, after such drying, usually brings the snail rapidly out of its shell and into full activity. The duration of desiccation, without death, has not been determined. Large specimens of the snail, taken in August from Soochow to Peking, were in a dry state for two days, but quickly emerged when immersed in water. Of another lot, consisting only of small specimens, nearly all died. Water seems to be important in the reactivation of desiccated specimens, and may be necessary for it. In its natural habitat the snail probably depends upon rain, dew, or the washing of water on the shore, for its return to activation. Comparison of the habits of *Oncomelania hupensis* with those of *Katayama nosophora* shows a close similarity, and therefore partly explains the ability of the two snails to act as the intermediate host for the same parasite.

TABLE 1.

	Katayama nosophora from Katayama.	*Oncomelania hupensis* from Soochow District
Average length of 100 individuals	7.1 mm.	6.4 mm.
Average breadth of 100 individuals	2.9 mm.	3.0 mm.
Ratio of breadth to length	1 to 2.45	1 to 2.1
No. of coils to spiral	8	7
Surface of shell	smooth	ribbed
Density of shell	fragile	hard

The superficial differences which we have observed between the two types of snail are all related to the shell. These differences are shown in Table 1.

The biological identity of the Chinese and Japanese forms of *Schistosoma japonicum.*

In a former experiment, already mentioned, we succeeded in infecting specimens of *Katayama nosophora* from Japan with miracidia from a Chinese patient with schistosomiasis. The miracidia had developed into mature cercariae within the snails in a period of about ten weeks. This led us to assume that the Chinese and Japanese forms of the parasite were biologically, as well as morphologically, identical. In order to establish this fact completely, however, it was necessary to perform the converse of the above experiment. This was particularly important, since we had found an intermediate host for the parasite in China, which belonged to a different genus than that of the Japanese host.

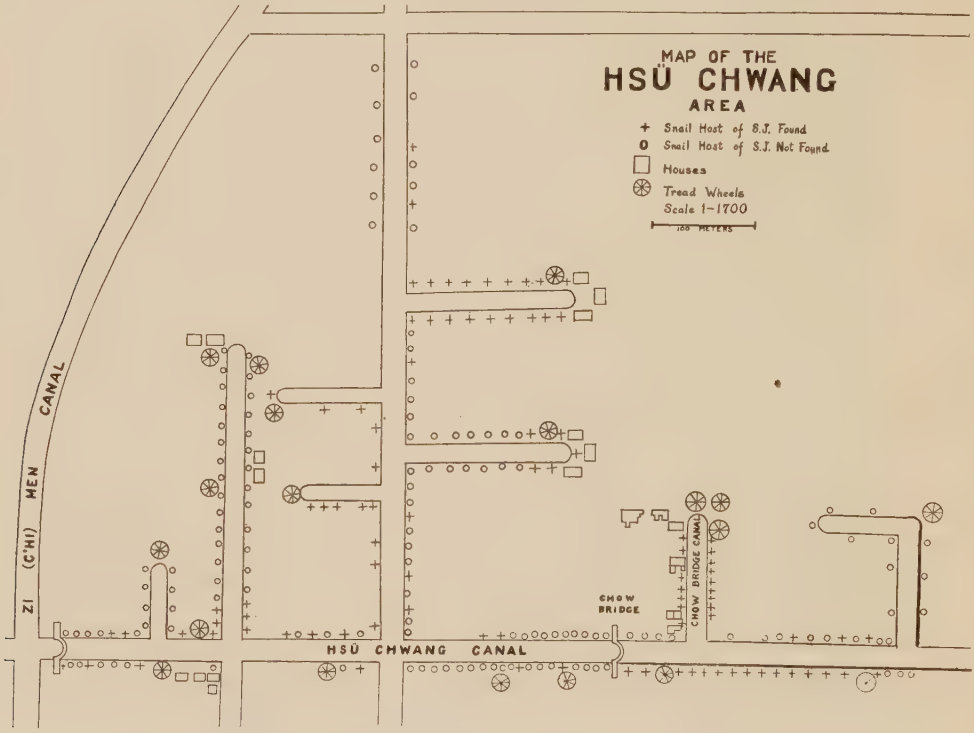
We therefore exposed about two hundred specimens of *Oncomelania hupensis* to miracidia obtained by hatching eggs from feces of a dog harboring the Japanese form of the worm. A few of these Oncomelania snails were killed one hour after exposure to the miracidia, and were examined in serial sections. Miracidia were found attached to various portions of the body, especially to the gills, and a few had apparently penetrated into the lymphatic spaces beneath the gill epithelium. The remaining snails were placed in moistearth, where they were left for ten weeks. At the end of that time they were immersed in water for two days, but none of them discharged cercariae. Fifty snails were then crushed, but no cercariae or secondary sporocysts could be seen. The remaining snails were, therefore, placed in moist earth again. Eleven weeks later, that is, twenty-one weeks after exposure to the Japanese miracidia, the thirty-seven snails which remained alive were again placed in water. Within twenty-four hours one of these began to discharge mature cercariae of *Schistosoma japonicum.* All of the snails were then crushed, and seven more were found to contain maturing secondary sporocysts of the parasite. Eight, therefore, out of thirty-seven, or 21 per cent., were infected with *Schistosoma japonicum.* The specimens of Oncomelania, used in this experiment, were collected from within the city of Soochow, where we had previously found no snails infected among four hundred examined. It is evident, therefore, that we infected Chinese snails with the Japanese form of the parasite and have established the bio-

logical identity of the two forms of the parasite. We are unable to explain the delay in maturation of the cercariae in the snail. The fact that the experiment was performed during the winter may have been one factor in the delay. Another reason may have been that the snails were immersed in water only once during the twenty-one weeks after exposure to the miracidia.

Distribution of the snail and of the disease.

Oncomelania hupensis is not ubiquitous over the areas where it is prevalent. In this it differs from most of the snails of this region, which will be mentioned later. In the brief time at our disposal for this search, only a small amount of territory could be carefully surveyed for the presence of the snail. An area of about one square Chinese li (71 acres, 0.28 sq. km.) was selected, extending west and north from the region where the snail was first discovered. This included the territory west, as far as the main Ch'i (Zi) Men Canal, and north to the next east-west secondary canal. Textfigure 1 shows this region with its canals and the localities in which the snail was searched for. The search was made by examining the banks of the canals every twenty to forty meters, sometimes from the shore, sometimes from a row-boat. As the banks of the canal varied continually in slope and in amount of vegetation, only spots which experience showed were likely to contain the snail were examined. It will be seen that, in the area thus surveyed, there were three canals in which the snail was not found, except that it was present at the mouth of one of these. Along the large secondary and tertiary canals it was found rather sparsely at scattered points, whereas it was much more abundant in the small terminal canals in which it was present. The small canal just east of "Chow's Bridge" is the one in which the snail was first found. The group of houses near this canal housed forty-one people. From the eight fecal examinations allowed us by these people, four were positive for schistosome ova. Two other clinically positive cases were negative microscopically. Several other persons, who were clinically very suspicious, could not be persuaded to allow a fecal examination. Since some of the persons whose feces were positive were clinically well, we feel sure that at least 50 per cent. of the inhabitants of this group of houses, and possibly 75 per cent., are infected with *Schistosoma japonicum*. Lack of time made it impossible to examine the inhabitants of other groups of houses in this area. The feces of one dog, two oxen and one water buffalo were examined for schistosome ova, with engative results. One emaciated dog was autopsied, but failed to show any evidences of schistosome infection.

Outside of the area in which the intensive survey was made, the Oncomelania was searched for at a few scattered points, in order to gain a rough estimate of its distribution in the general neighborhood of Soochow. From Textfigure 2 it will be seen that the snail was found in small branches of the Ch'i Men Canal, nearly as far south as the city wall of Soochow. In most of the canals a small percentage of the snails were infected. This was true in one canal which was imme-

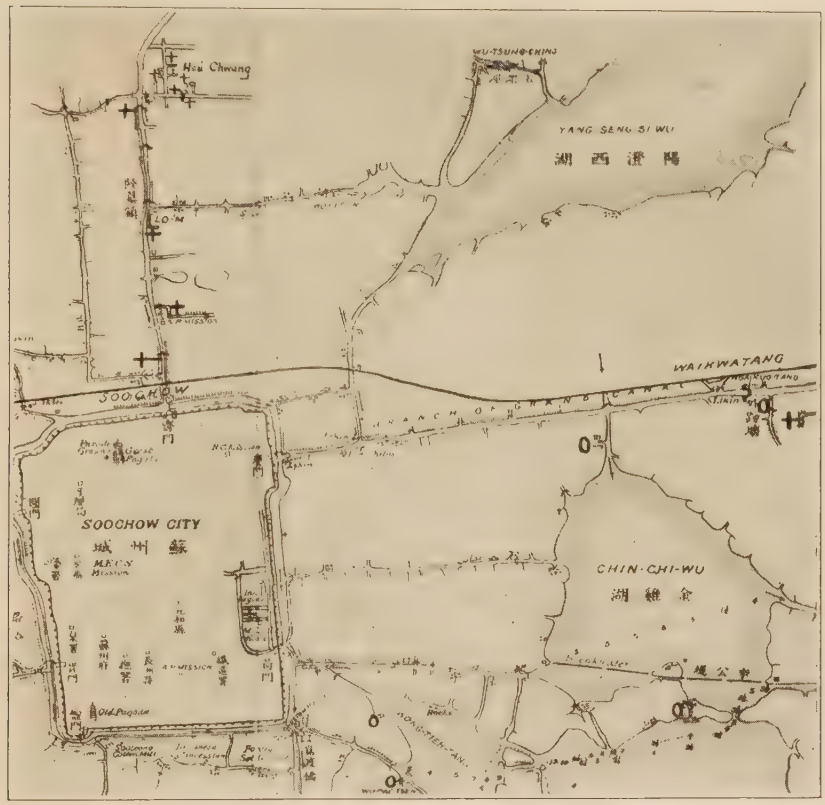


TEXTFIGURE 1. Map of the Hsü Chwang Area, in which the shores of all the canals were searched intensively for *Oncomelania hupensis*.

diately adjacent to the Elizabeth Blake Hospital of the Southern Presbyterian Mission. Within the city of Soochow Oncomelania was found in a canal within three hundred meters of the Soochow Hospital. Here no cercariae of *Schistosoma japonicum* were found in the four hundred snails which were examined, but we succeeded in infecting snails from this locality in the laboratory.

Endemic centers of schistosomiasis exist in some of the villages on the shores of lakes about Soochow, but were too far away to be visited

conveniently. The shores of one lake were examined, as well as canals in villages on the lake shore, but no Oncomelania snails were found. We did, however, find the snail in an irrigation ditch between rice fields near the town of Wai Kwa Tang, ten miles east of Soochow. This ditch, which was about a meter wide and a half meter deep, was



TEXTFIGURE 2. Map of Soochow and environs, showing the main canals and the localities in which a search was made for *Oncomelania hupensis*. + indicates *Oncomelania* found; *0*, *Oncomelania* not found.

leading water from a spring in the middle of the rice field area to a neighboring canal. The rice fields were separated from this ditch on each side, but were only a few inches above the level of its water. Oncomelania was found on the banks of this ditch in very large numbers. It was also found in the adjacent rice fields at one point where the ditch led directly into the fields. Although no schistosome cer-

cariae were found in the three hundred of these snails which were examined, the snails were vigorously attacked by miracidia of *Schistosoma japonicum* in the laboratory, and, seventy-four days after exposure, serial sections of one of these snails showed mature cercariae of the parasite.

We have said little about searching in the rice fields for the Oncomelania. As soon as we discovered that the rice fields were moistened only by rain or by mechanically raising the water from the canals, and that they rapidly became dry at other times, it was realized that such a locality would be unfavorable for the existence, at least at that time of the year, of any snail which needs moisture for the continuance of its activity. Nevertheless, wherever the fields were moist or their locality seemed at all favorable for the snail, it was searched for, but without success except in the one instance cited above. This does not exclude the possibility, however, that in wet seasons of the year, when the fields are continually under water, the snails may climb into the rice fields. This is also probable in districts where the canals are fed from rivers, and where the fields are below the level of the canals and are therefore usually wet. This is the condition which exists in the Katayama district in Japan, where the snails inhabit the rice fields and the ridges between the fields. If the snails do reach the rice fields during the wet seasons, in districts similar in topography to the country about Soochow, the question remains, whether in dry seasons they die, or return to the canals, or become buried in the soil. This question is important in connection with the infection of the snails by schistosome miracidia at times when fresh fecal material may be used on the fields for fertilizer. If the snails are limited to the canals in some large areas like that around Soochow, the problem of their destruction is much simpler than if they are present, at times, also in the rice fields. In order to settle this question, the rice fields adjacent to infected canals should be observed in all seasons of the year.

Other gasteropods encountered.

We are not prepared to describe in detail the other gasteropod molluscs met with in this search, but will mention them briefly as a matter of record. These snails have also been classified for us by Mr. Bryant Walker. The snails best known to the people of the district are various species of the genus *Vivipara* (Fig. 14, *a* and *b*), which are present in all the large and small canals, and are dredged by fishermen in immense numbers from the bottoms of large canals. The larger specimens, often 4 cm. in diameter, are eaten by the people after being

cooked, the smaller ones are taken away to be used as food for fish. The smaller members of this genus were found near the shore of, and in dredgings from the canal, where *Oncomelania hupensis* was first found. They often cling to the stone walls of the larger canals just at or beneath the surface, but rarely emerge from the water.

The only snail which, in this region, may be mistaken for the *Oncomelania* is its larger distant relative *Melania cancellata* (Fig. 14*c*). The smallest forms of this very widely distributed snail, which we encountered, were about the same size as the largest specimens of *Oncomelania hupensis*, and the proportions of the two shells corresponded quite accurately. Careful observation easily distinguishes the two snails, however, for the "costules" of *Melania cancellata* are farther apart and more prominent than those of *Oncomelania hupensis*, and the shell is much thicker and somewhat lighter in color. The largest specimen of *Melania cancellata* which we found measured 21 mm. in length. Except for the shells of dead individuals, this snail was always found beneath the surface of the water, so that it differs decidedly in its habits from *Oncomelania hupensis*. It was never found in large numbers. It was encountered both in canals and on the shore of lakes.

A third common snail in this region is the genus *Lymnaea* (Fig. 14*d*) of which a number of species were found. They measured from 5 to 15 mm. in length. They were found in canals of all sizes, living a short distance below the surface of the water, on stones or water grass. During a rain they were seen to creep far up the wet wall of a large canal. At other times they rarely left the water.

Quite different from any of the other snails encountered was *Clausilia frigida* (Heude) (Fig. 14*e*). This is a land snail, but was found on the stone pier of a bridge over a canal, in a village, just off the Wang Tieh Lake.

Two species of *Bythinia* were encountered, namely *B. longicornis* (Fig. 14*f*) and *B. striatula* (Fig. 14*g*). Each averaged about 8 mm. in diameter. They were found a short distance below the surface of the water of canals, on stones or grass, but did not appear to approach the surface as much as the other snails.

Several specimens of *Planorbis* (Fig. 14*j*) were found, all of which were small forms, never measuring over 5 mm. in diameter. They live usually just beneath the surface of the water, but are often deeper, and are found mostly on blades of flat water grass or on stones. They rarely emerge from the water.

With the exception of *Clausilia*, a number of individuals of each of these genera were examined for the presence of cercariae, as follows:—

Vivipara 77, *Planorbis* 50, *Lymnaea* 72, *Bythinia longicornis* 396, *Bythinia striatula* 119, *Melania cancellata* 781. In none of these snails were cercariae found which were morphologically similar to that of *Schistosoma japonicum.* Other types of cercaria were found in some of the species, including two types with forked tails. Both of these types were much larger than the cercaria of *Schistosoma japonicum,* beside having other distinguishing features. They will be described in another communication.

In order to further exclude the probability that these snails could act as the intermediate host for *Schistosoma japonicum,* we exposed specimens of *Planorbis, Lymnaea, Bythinia* and *Vivipara* to infection by miracidia of *Schistosoma japonicum.* Under the microscope miracidia were observed to approach and become attached to each of these types of snail, in the same manner in which they approached *Oncomelania hupensis.* But the activity of the miracidia did not appear to be so great in the presence of these other species. Specimens of these various types which had been exposed to miracidia were killed at intervals of from one to five days after exposure, but serial sections failed to reveal any miracidia in their tissues.

Acknowledgments.

We wish, in closing, to express our thanks to Dr. John A. Snell, director of the Soochow Hospital, who placed his laboratories and equipment at our disposal, and who conducted us to the endemic area and gave much of his time and thought to the progress of the research. We are also indebted to several members of the staff of the Soochow Hospital for cooperation in the work, and to Dr. M. P. Young, director of the Elizabeth Blake Hospital, for placing his motor boat at our disposal and for allowing us the use of his laboratories. Dr. Woo Kwang Ming, of the Elizabeth Blake Hospital also assisted us by examining many specimens of various snails for the presence of cercariae. We take occasion also to express our appreciation to Mr. Bryant Walker who classified for us *Oncomelania hupensis* and the other snails collected during our search.

Summary.

1. The intermediate host of *Schistosoma japonicum* in China had never before been identified.

2. In the region about Soochow, Kiangsu Province, we found that *Oncomelania hupensis* Gredler acts as the intermediate host for this parasite.

3. Proof of this was obtained by successfully infecting mice with

the cercariae obtained from this snail, and also by successfully infecting this snail with miracidia of *Schistosoma japonicum*.

4. The biological identity of the Chinese and Japanese forms of *Schistosoma japonicum* was established by infecting *Katayama nosophora*, the intermediate host in Japan, with material from a Chinese patient; and by infecting *Oncomelania hupensis*, the intermediate host in the Soochow region, with material from a dog who harbored the Japanese form of the worm.

5. No other snail was found in the Soochow region which acted as intermediate host for *Schistosoma japonicum*.

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EXPLANATION OF FIGURES (PLATES XVI–XVIII).

FIG. 1. Irrigating treadwheel near Soochow, rotated by human footpower.

FIG. 2. Treadwheel rotated by water buffalo.

FIG. 3. A typical village in the rice country near Soochow. The houses are close to a terminal canal. Fifty to seventy-five per cent. of the inhabitants are infected with *Schistosoma japonicum*.

FIG. 4. The first clinical case of schistosomiasis encountered during our search for the intermediate host. Note the distended abdomen, typical of the late stage of the disease.

FIG. 5. The terminal canal on the shore of which we first found *Oncomelania hupensis*, containing the cercariae of *Schistosoma japonicum*. This canal is typical of all those where the snail was found in this area.

FIG. 6. Cercaria of *Schistosoma japonicum*, obtained from *Oncomelania hupensis*. × 210.

FIG. 7. Mature male and female *Schistosoma japonicum*, obtained from a mouse, 31 days after infection by cercariae from *Oncomelania hupensis*. × 10.

FIG. 8. Miracidium of *Schistosoma japonicum* in subcuticular tissues of *Oncomelania hupensis*, 20 days after infection. × 220. *M* = miracidia.

FIG. 9. Primary sporocyst in lymphatic space, near intestine, of *Oncomelania*, 27 days after infection. × 220. *S* = sporocyst.

FIG. 10. Immature cercariae of *Schistosoma japonicum* in secondary sporocysts, in hepatic lymph spaces, of *Oncomelania*, 55 days after infection. × 220. *S* = sporocyst, *C* = cercaria.

FIG. 11. Nearly mature cercariae in lymph spaces of liver of *Oncomelania*, 69 days after infection. × 220.

FIG. 12. *Oncomelania hupensis* Gredler, intermediate host of *Schistosoma japonicum*, in the Soochow region. Above, × 5; below, × 1.

FIG. 13. Type of canal bank most favorable for *Oncomelania hupensis*. Note rice field above.

FIG. 14. Snails encountered in the search for the intermediate host of *Schistosoma japonicum*. × 1. *a* and *b*, *Vivipara*; *c*, *Melania cancellata*; *d*, *Lymnaea*; *e*, *Clausilia frigida*; *f*, *Bythinia longicornis*; *g*, *Bythinia striatula*; *h*, *Oncomelania hupensis*; *i*, *Katayama nosophora* (introduced for comparison); *j*, *Planorbis*.

B. THE DISCOVERY OF THE MOLLUSCAN INTERMEDIATE HOST OF *Schistosoma joponicum* IN THE KASHING AREA.

(Plate XIX.)

The search for the molluscan intermediate host of *Schistosoma japonicum* in the region of Kashing, Chekiang Province, China, was made in order to supplement the investigations in the Soochow area. Kashing lies on the Grand Canal, midway between Soochow, on the north, and Hangchow, on the south. It is the center of a large number of intercommunicating canal systems extending in many directions, but particularly common to the southeast of Kashing. The city is also on the main rail line between Shanghai and Hangchow.

Kashing is in a region of rice farming, in many respects similar to that of Soochow. In the Kashing area, however, mulberry trees, used in feeding silk worms, are more common than in the Soochow district.

Kashing has been known as a heavy center of schistosomiasis for a number of years. A large number of medical cases in the Presbyterian Mission Hospital at Kashing are persons infected with this disease. Map III (section V of this monograph) shows the general distribution of schistosomiasis in this area. In view of the common topographic features of the Kashing and Soochow districts, and the similar agricultural pursuits of the two regions, it was a matter of importance to determine if the molluscan intermediate host of schistosomiasis in the two areas was the same, or if it was different.

The trip to the infected district near Kashing in which the search was made, came late in March 1923, just as spring was coming on. In company with Doctor F. R. Crawford, director of the Presbyterian Mission Hospital, of Kashing, we proceeded north by motor boat for

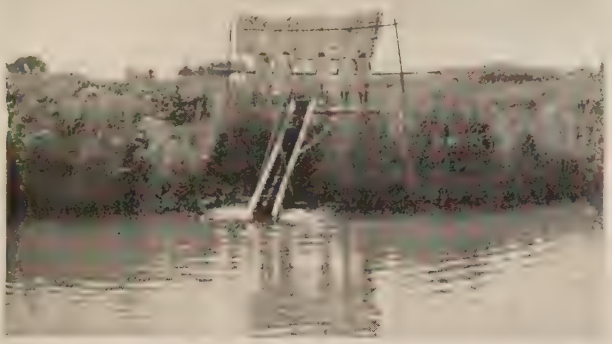


Fig. 1

Fig. 4

Fig. 2

Fig. 3

(Faust and Meleney: Studies on Schistosomiasis Japonica, IV.)

Fig. 6

Fig. 7

Fig. 5

Fig. 13

(Faust and Meleney: Studies on Schistosomiasis Japonica, IV.)

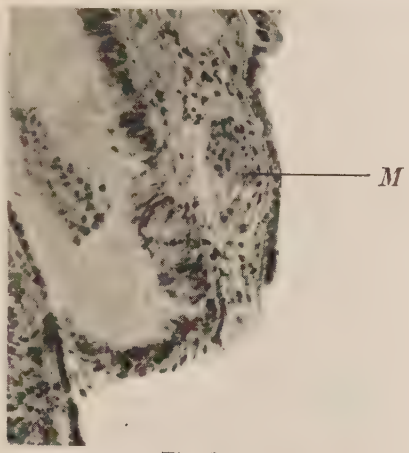


Fig. 8

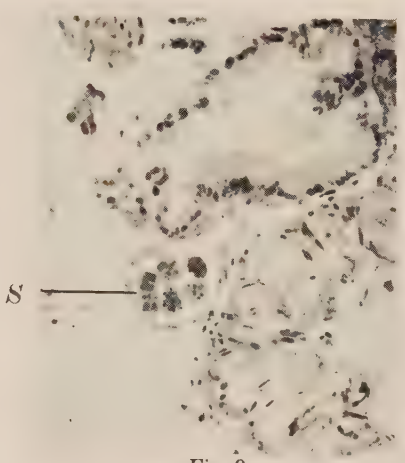


Fig. 9

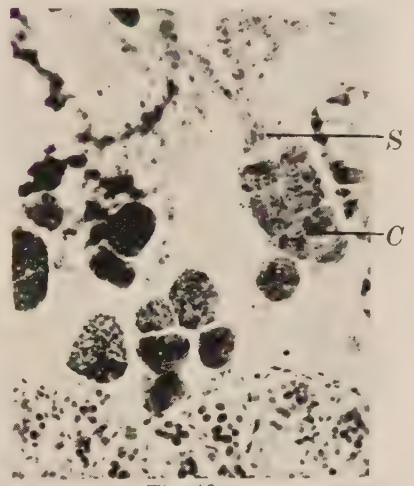


Fig. 10

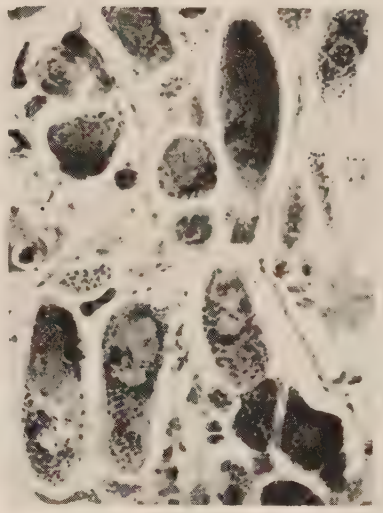


Fig. 11

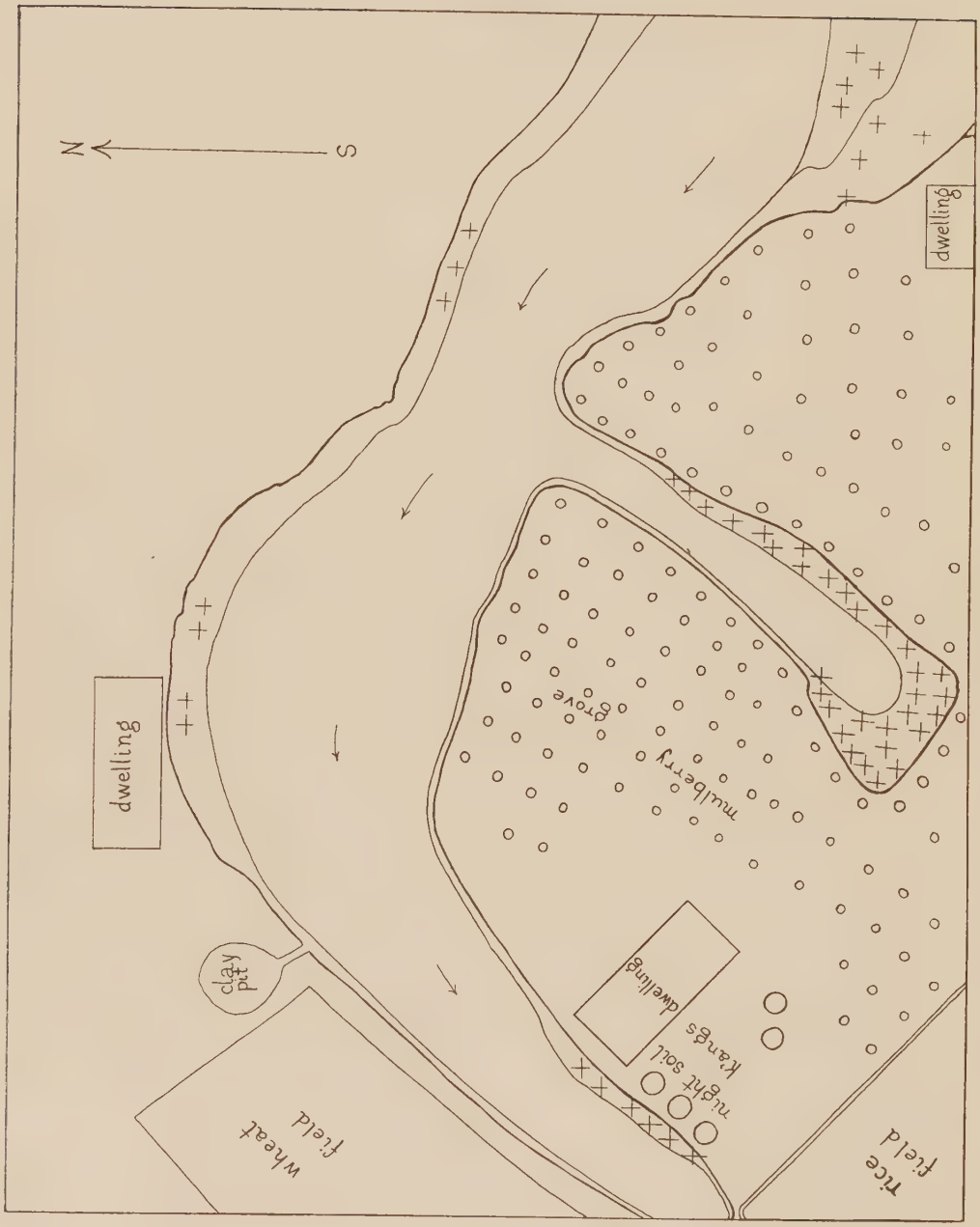
Fig. 12

Fig. 14

(Faust and Meleney: Studies on Schistosomiasis Japonica, IV.)

some ten miles up the Grand Canal from Kashing, then turned into a lateral canal toward the village of Yang Miao Ch'en, from which vicinity cases of schistosomiasis were known to have come to the Kashing Hospital. We stopped on the near side of the town and entered a terminal canal, which appeared to have the general characteristics of the infected canals around Soochow. A careful search for two hours along the banks of the canal, in the silt pits and in the rice fields adjacent to the canal, failed to reveal either living or dead specimens of any mollusc except pond types, and in the particular hamlet by the side of the canal no clinical cases of the disease were observed. It was noted that the soil in this region consisted of a hard-pan clay, and that sun-dried bricks and pottery were abundant. Such soil, it seemed probable, could not support the snail hosts during the winter months, for they could not get under cover of the outer layer for protection against the cold. We then proceeded through the village of Yang Miao Ch'en to another hamlet on the banks of a secondary canal, and there, in loose, moist humus-soil, at the water level on the banks of the terminal and secondary canals, many thousand specimens of *Oncomelania hupensis*, the snail involved in the Soochow infection, were found. On the return trip to Kashing several stops were made at points on the Grand Canal, where protected coves and backwater were found, but the soil was without exception clayey in character, and no Oncomelanias or related molluscs were found. The snails collected were examined for infection, but were found to be negative. They were taken to Peking for further study.

Careful examination of the sketch map of the locality in which the Oncomelania snails were found (Textfigure 3) will disclose several important points bearing on the conditions under which these snails existed. The banks of the secondary canal were steep and came directly to the water's edge except at four places, where there was a shallow sloping beach consisting of gravel and decaying vegetable matter. In each of these four places the snails were found. The terminal canal, in which the greater number of specimens were collected, was an inpocketing of the secondary canal. It was steeply banked along the outer half and had sloping sides toward the inner portion. The soil consisted of a loose humus, from which water oozed whenever anyone stepped over it. No snails were collected along the outer half of the terminal canal, but several thousand individuals were secured at the inner end. The exact character of the surroundings is indicated in the photographs taken at several spots where collections were made (Figs. 1, 2, 3, 4). Furthermore,



TEXTFIGURE 3.

Sketch map of the region near Yang Miao Ch'en, where *Oncomelania hupensis* was found. + indicates where the snails were found.

it can be seen that the ground between the secondary canal and the terminal canal was planted to mulberry trees. To the south of this there was a rice field (see textfigure). Careful search in the rice field revealed neither living specimens of *Oncomelania hupensis*, nor dead shells of this snail. On the northeast side of the secondary canal there was a wheat field and a clay pit. The soil here was noticeably harder and of a different consistency, containing little or no humus. There was one house, just opposite the terminal canal, and several dwellings to the right, and a house of three rooms to the left, between the secondary and terminal canals. Several inhabitants of this place were clinical schistosome cases. In the dooryard of this dwelling were five large, uncovered earthenware k'angs for the reception and ripening of nightsoil (see photograph, Fig. 5). Three of these were immediately on the canal bank and slopped over into the canal. Several snails were found at this point. Promiscuous defecation was observed in the mulberry grove which drained into the terminal canal (see photograph, Fig. 6).

While some snails were found under decaying leaves and small bits of debris, most of them were still buried in the moist loose soil, in which they had been hibernating during the winter. The fact that the snails were not infected at this time of the year was not surprising, since they were just coming out from their winter cover. When some of these snails were later submitted to an infection of miracidia of *Schistosoma japonicum*, in the laboratory in Peking, they were vigorously attacked and were later found to harbor the infection.

Discussion.

The investigation to discover the molluscan intermediate host of *Schistosoma japonicum* in the region of Kashing not only lead us to the discovery that the intermediate host of the infection in the region was the same as that of the Soochow area, but provided additional facts regarding the bionomics of the snail. The edaphic conditions in the Kashing district surveyed were similar to those of the Soochow region investigated. The snails were found neither in the rice fields nor in the waterways of the main canals. Nor were they found along the hard packed slopes of the Grand Canal or secondary canals where only grass was abundant. The snails were found in secondary as well as terminal canals, where the wash of the stream was not sufficient to carry off humus and decaying debris. This type of environment provides an excellent opportunity for infected nightsoil, seeping down from the ground above, to be diluted, and to allow the miracidia to

hatch out and infect the snails. Boatmen and farmers, including children, in such a locality, are then subjected to the infection, the period of exposure in such a region lasting from spring until late fall. Such an endemic cycle is found, no doubt, in thousands of spots in the Kashing district, where similar conditions prevail.

It is of importance, in passing, to note that the water system in the Soochow and the Kashing areas is the same, namely, the Grand Canal and subsidiary canals, all on about the same level, with no appreciable direction of flow. Throughout this waterway system no specimen of Katayama has yet been found, and it is our belief that there is a direct relation between the type of water system found and the molluscan species carrying the infection.

ACKNOWLEDGMENT.

In conclusion, we wish to thank Doctor F. R. Crawford, of Kashing, and other members of the Presbyterian Mission at Kashing, for their help in making the survey of this region possible.

SUMMARY.

1. The search for the molluscan intermediate host of *Schistosoma japonicum* in the region of Kashing, Chekiang Province, was made to supplement the survey in the Soochow area. Large numbers of *Oncomelania hupensis* were found on the banks of a secondary and a terminal canal near Yang Miao Ch'en, in loose, moist humus and under decaying vegetable debris.

2. *Oncomelania hupensis* was found neither in the rice fields of this region nor along the clay banks of the secondary or lateral canals. The fact that the rice fields are inundated only a part of the year explains why the snails were not found there, and the character of the clay soil, which does not permit the snails to seek a winter cover by boring into it, is responsible for the absence of these molluscs along the clay banks.

3. Although these snails which were collected were uninfected, when subjected later to an experimental infection in the laboratory, they were vigorously attacked by miracidia of *Schistosoma japonicum*, and were later found to be infected.

4. The local conditions under which *Oncomelania hupensis* was found are conducive to the hatching of the miracidia of *Schistosoma japonicum* and to the infection of the snails.

5. There is probably a close correlation between the type of water supply in the Grand Canal waterway system and the existence of *Oncomelania hupensis* as intermediate host of the infection in this area.

Fig. 1

Fig. 2

Fig. 3

Fig. 4

Fig. 5

Fig. 6

(Faust and Meleney: Studies on Schistosomiasis Japonica, IV.)

EXPLANATION OF FIGURES (PLATE XIX.)

Figs. 1 to 4. Views of the terminal canal near Yang Miao Ch'en, where *Oncomelania hupensis* was found.

Fig. 5. Type of nightsoil k'ang used in the region where the survey was made. The k'angs slopped over onto the sides of the secondary canal, where the snails were abundant.

Fig. 6. Mulberry grove in the surveyed district between the secondary and terminal canals.

C. THE DISCOVERY OF THE MOLLUSCAN INTERMEDIATE HOST OF *Schistosoma japonicum* IN THE SHAOHSING AREA.

(Plate XX.)

In connection with an investigation of the geographical distribution of schistosomiasis japonica in the vicinity of Shaohsing, Chekiang Province, China, in February and March 1923, a search was made for the intermediate molluscan host involved in the infection. The discovery of this host and the bearing on the problem of schistosomiasis japonica in China are presented in this portion of the paper.

Shaohsing is a large inland city, lying in the mid-northern portion of the Chekiang peninsula, south of Hangchow Bay. It is connected by waterways in all directions. The water supply of the region comes from the hills to the southwest of Shaohsing and flows in a northeastern direction through the city to a point about ten miles beyond, where its discharge into Hangchow Bay is regulated by a coffer-dam with flood gates. While the water utilized for irrigation on the plain is elevated to the rice fields by footpumps, that in the surrounding valleys has a considerable fall, allowing the fields to be irrigated from above, without the need of foot-treads. In addition to rice cultivation, a large variety of farm and garden crops is raised in this area.

The valleys in the districts surrounding Shaohsing are dissected by many canals which, during the period of high water, have a marked current. This is in direct contrast to the Soochow-Kashing water supply. The valleys are shut in on three sides by numerous hills, which serve as burial grounds and have many shade trees.

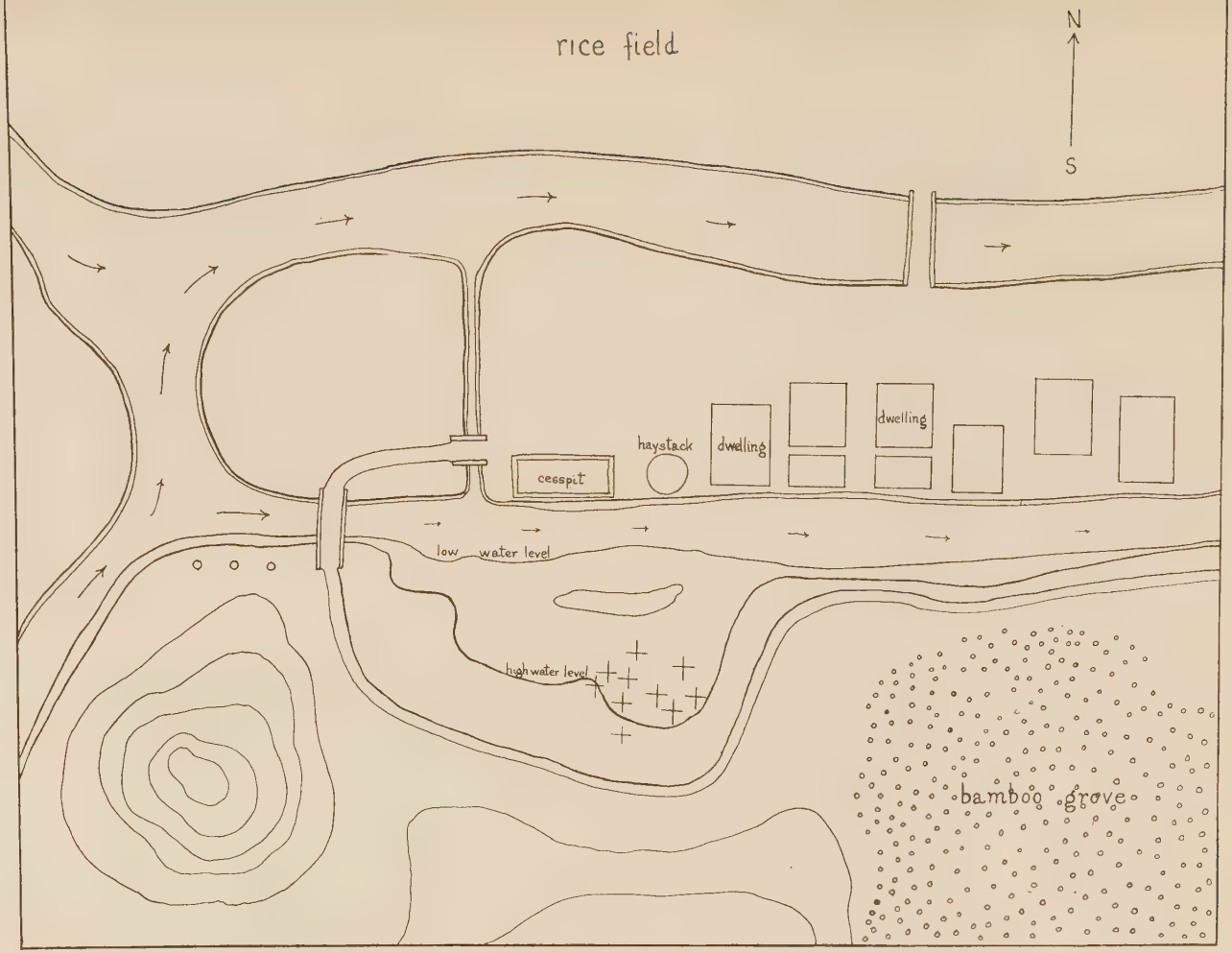
In company with Doctor C. H. Barlow, of the Shaohsing Christian Hospital, we made a trip up one of these valleys on March 15, 1923, to the village of Ch'en Chia Chiao, about three and a half miles from the southwest corner of Shaohsing City. Cases of schistosomiasis japonica from this region were on record in the Shaohsing hospital. After passing through the waters of the plains and entering the main current of the valley stream several stops were made to search for

snails, but none were found except the ubiquitous *Melania cancellata*, *Vivipara quadrata* and Lymnaea sp. At the village of Ch'en Chia Chiao the main stream was diverted around the north side of the settlement while the smaller supply of water passed under a short stone bridge before coming alongside the village (see sketchmap, Textfigure 4). This bridge not only served to divert the greater share of water into the main stream but provided a bit of backwater on its lower side. Just opposite the village there had developed a small cove with a pebbly beach. Rising up midway there was an embankment (Fig. 1) marking the high water level, while slightly farther back was the main embankment. Opposite this cove there was a small connecting canal. In the southwest corner of the village a large rectangular stone cesspit had been placed for the reception of the village nightsoil (Fig. 2). It was not water-tight and considerable seepage was observed to be trickling out the sides and bottom.

Search for the schistosome snail was undertaken in the backwater of the cove, just below the stone bridge, since the position of this locality opposite the village offered a favorable place for the development of snails which might be infected with *Schistosoma japonicum*. The beach along the line of low water level was strewn with shells of ordinary water snails, but on the intermediate ground of moist humus and moss numerous specimens of a snail, recognized as a Katayama, were found. These snails have been kindly identified for us by Doctor Nelson Annandale, who reports them to be *Katayama nosophora*. The specimens collected were all taken from mossy banks or underneath the moss in the porous humus or loose wet mud. Both living snails and dead shells were found in this locality, but in the clay banks above the stone bridge, where there was no moss, the Katayamas were absent. The accompanying photographs (Figs. 3, 4) indicate the exact conditions under which the snails were found.

The Katayamas were placed in a clean bottle and taken to Shaohsing, where two hours later they were emptied into a small aquarium two-thirds full of water. Two hours later an examination of the surface film revealed fork-tailed cercariae, which microscopic examination proved to be the cercariae of *Schistosoma japonicum*.

Later in the month of March Doctor Barlow made a trip into the adjacent valley, to the neighborhood of Lan Ting, where schistosomiasis was known to be present. In a similar mossy habitat many *Katayama nosophora* were obtained, which, however, proved on examination to be uninfected.



TEXTFIGURE 4.

Sketch map of the region of Ch'en Chia Chiao, in the Shaohsing area, where infected *Katayama nosophora* were found. + indicates where the snails were found.

Discussion.

The discovery of *Katayama nosophora* as the intermediate host of *Schistosoma japonicum* in the Shaohsing area is a matter of peculiar interest and importance, because species of Katayama serve as the only known intermediate hosts of the infection in Japan and Formosa. The question arises, therefore, as to why this genus of snail should act as intermediate host in certain localities while *Oncomelania hupensis* serves in that capacity in the Soochow-Kashing area. Although the solution to this question may involve facts not now in our possession, we believe the question to depend largely on the following conditions. In the first place, both these and possibly other closely related forms of operculate snails are capable of serving as intermediate hosts of *Schistosoma japonicum*. In early sections of this paper we have proved conclusively that both the Japanese and the Chinese infections will interchangeably infect *Katayama nosophora* and *Oncomelania hupensis*. The edaphic conditions required of these two groups of snails are essentially the same, but as yet the two genera have not been found in the same areas. The important difference in conditioning environment seems to lie in the type of water supply. The Oncomelania is found in water where the current is hardly, if at all perceptible. The Katayama lives near a supply of clear flowing mountain water. The topography of the Japanese and Formosan areas of infection is such that this hypothesis would apply to them as well as to the Chinese area investigated. While Oncomelania has not been reported from schistosome areas in Japan and Formosa, the distribution of this form in the Yangtze Valley is fairly coextensive with that of schistosomiasis japonica there, for Oncomelania species have been collected by French naturalists in Chekiang, Kiangsu, Anhwei, Hunan, Hupeh and Szechuan Provinces (Heude 1890), in the exact regions where the disease is most prevalent. It seems altogether likely, therefore, that the species of snail most heavily involved in the propagation of schistosomiasis japonica in China is Oncomelania, since this snail not only can exist, but actually has been found under conditions of water supply where the disease is most prevalent in China. Furthermore, it seems probable that all of the species of Oncomelania described by Heude (l. c.) are to be referred to the form, *Oncomelania hupensis*.

Acknowledgment.

We desire to thank Doctor Barlow and other members of the staff of the Shaohsing Christian Hospital for their kind assistance in the

Fig. 1

Fig. 2

Fig. 3

Fig. 4

(Faust and Meleney: Studies on Schistosomiasis Japonica, IV.)

examination of records and personal guidance which made this survey possible. We are also indebted to Doctor Nelson Annandale for his identification of the snail involved.

Summary.

1. The search for the intermediate host of *Schistosoma japonicum* in the Shaohsing area in the region of Ch'en Chia Chiao lead to the discovery of *Katayama nosophora* as the snail involved.

2. The mollusc was found in a mossy habitat between low and high water level, in a locality of loose moist humus, in a quiet cove near clear mountain water.

3. The type of water supply is believed to be directly correlated with the existence of Katayama. This hypothesis holds equally well for the species of Katayama found in Japan and Formosa.

4. The recorded presence of Oncomelania in all areas of heavy infection with schistosomiasis japonica in the Yangtze Valley together with the restricted environmental conditions under which Katayama can live, indicate that Oncomelania is much more heavily involved in the infection in China than is Katayama.

Literature cited.

Heude, P.

1890. Memoires concernent l'histoire naturelle de l'empire Chinois. Tome 1. Cahier 4. Notes sur les mollusques terrestres de la vallie du fleuve Blen, pp. 125–188, planches 33–43.

Explanation of figures (plate xx.)

Fig. 1. View of the embankment at Ch'en Chia Chiao, across from the village, showing low and high water levels.

Fig. 2. The nightsoil cesspit, opposite the locality where the Katayamas were found; a favorable source for infection of the molluscs.

Figs. 3 and 4. Views, showing the discovery of the snails at Ch'en Chia Chiao.

D. The discovery of Katayama in South China.

(Plate XXI.)

In view of a recent statement of Maxwell (1923) to the effect that schistosomiasis japonica was believed to be present in the West River valley above Canton, a trip was made in April, 1923, to Fatshan (Buddha's Mountain), some fifteen miles from Canton, in the upper region of the Pearl River delta, to study conditions relative to the disease in this region. After satisfying ourselves from conversation with physicians in the Wesleyan Mission Hospital at Fatshan and

from inspection of the hospital records that the disease had not been seen either in the delta region or in the West River valley, we searched in the surrounding villages for the possible presence of a schistosome intermediate host.

The main canals in this locality were bounded with squares of sun-baked mud, and the secondary canals which run through the villages were bordered with grasses, sedges and water hyacinth. In most of the canals the water at this time of the year was very low and there was considerable accumulation of vegetable debris, in among which Lymnaeas, *Vivipara quadrata*, and *Melania tuberculata* abounded. In the village of Tip Kan, about one mile from Fatshan, the banks of a secondary stream were covered at high water level with moss and loose moist humus. Careful search at this point (Textfigure 5) revealed numerous specimens of *Katayama nosophora*, as well as of the terrestrial form, *Opeas gracilis* (Hutton), kindly identified for us by Doctor Nelson Annandale. The local conditions under which the snails existed (Figs. 1, 2) corresponded closely to those prevailing in the Shaohsing area. Except at times of low water the streams in this district have a noticeable current.

On examination the Katayamas all proved to be uninfected.

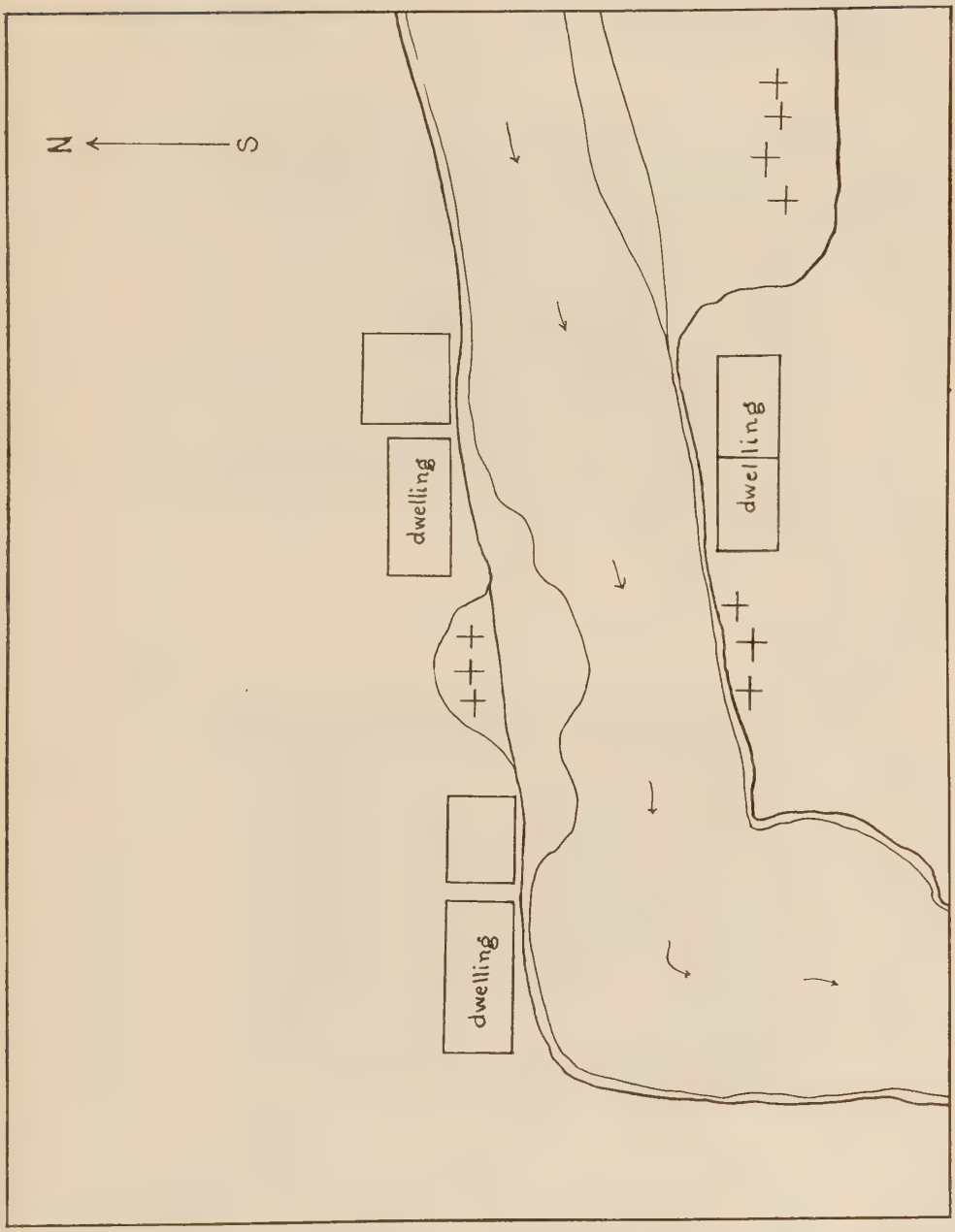
Discussion.

The discovery of a snail, *Katayama nosophora*, of the same species as that involved in the schistosome infection in the Shaohsing area, in the Pearl River delta, provides proof of the possibility of the introduction of schistosomiasis into this district. While no infection is now on record for this vicinity, the presence of the disease in the North River valley, near Shuichow, which water system flows into the delta, makes the establishment of the infection in the delta more than a remote contingency.

It may be stated, therefore, that danger exists of the introduction of schistosomiasis japonica into this region where it is not now known to exist, but where conditions favor the development of the intermediate molluscan host, and where a fortuitous combination of circumstances could easily bring infected individuals and these snails within the same endemic cycle.

Acknowledgment.

We wish to express our gratitude to Doctor W. W. Cadbury, physician to the Canton Christian College, and to thank the staff of the Wesleyan Mission Hospital, Fatshan, for their assistance in this



TEXTFIGURE 5.

Sketchmap of the canal and surroundings in the village of Tip Kan, near Fatshan, where *Katayama nosophora* was found.
+ indicates positions where the snails were found.

investigation; we also wish to thank Doctor Nelson Annandale for identifying the snails involved.

Summary.

While schistosomiasis japonica is not known to exist at the present time in the Pearl River delta or in the West River valley above Fatshan, the discovery of the mollusc, *Katayama nosophora*, in this region makes the introduction of the disease, present in a neighboring river valley, more than a remote possibility.

Literature cited.

Maxwell, J. L.
1923. Historical aspects of schistosomiasis japonica. China Med. Jour. In press.

Explanation of figures (plate xxi).

Figs. 1 and 2. Views of the bank of the canal at Tip Kan, near Fatshan, where *Katayama nosophora* was found.

Fig. 1.

Fig. 2.

(Faust and Meleney: Studies on Schistosomiasis Japonica, IV.)

V. THE DISTRIBUTION OF SCHISTOSOMIASIS JAPONICA IN THE ORIENT.

(Maps 1 to 5.)

Introduction.

Schistosomiasis japonica is confined to the Far East. No case is on record that is known to have been contracted outside of the endemic areas in Japan, China, Formosa and the Philippines. In Japan the endemic centers are fairly well defined. They occur on the main island, along the Ashida River, a few miles back from the coast in the Katayama district of Hiroshima and Okayama prefectures; in two districts near Mt. Fuji, one to the north at Koofu, in the Yamanashi district, and one on Lake Ukishima, near the coast at Numazu (Shizuoka prefecture); and in the Tone River district, a few miles northeast of Tokio (Ibaraki prefecture). Another endemic center is found on the Island of Kyushu, near Kurume, on the Chikugo River (Saga prefecture). All of these endemic centers are relatively small areas but are heavily infected (see map 1).

Not only have epidemiological surveys of these regions been made to determine the incidence of infection of the disease among the population, but in the Katayama basin and in the infected area of Kyushu Province careful investigations have been made to determine the exact distribution of the molluscan host.

In the Philippines the infection has been determined through the examination of prisoners in Bilibid Prison who come from all parts of the Islands (Garrison, 1908). It is described as being present in the southern group of islands, Leyte, Samar and Mindanao, and has been diagnosed in prisoners who gave their birthplace as Luzon, Panar and La Union. More recent examinations of the same type of subjects seem to indicate, however, that a possible error has been made in compiling the original information, since only prisoners from the islands of Samar and Leyte have been positively proved to harbor the infection (Mendoza-Guazon, 1922).

In Formosa an endemic center of schistosomiasis has been located by Yokogawa (1915) in the vicinity of Shinchiku, near the center of the Island, where man, cattle, oxen, dogs and hogs are said to be infected. Specimens of cercariae and adults, which Doctor Yokogawa has been

MAP 1. Distribution of schistosomiasis japonica in Japan. Oval areas indicate the regions of endemicity.

kind enough to send to us, are morphologically identical with *Schistosoma japonicum.*

In China, following the discovery of Katsurada in 1904, reports of the infection were published for Hunan (1905), Anhwei (1907), Hupeh (1910), Kiangsu (1910), and Kiangsi (1910) Provinces. These data were later assembled under the direction of the Research Committee of the China Medical Missionary Association and published first, in briefer form, in the China Medical Journal (1910, 1910a), and later, more extensively, in Jefferys and Maxwell's "The Diseases of China" (1911). At that time, aside from the two records from Hongkong, which were not emphasized as important because of Hongkong's trade relations with other parts of the Orient, the infection in China was believed to be confined to the central and lower Yangtze Valley, between parallels 28 and 36, north latitude, and from meridian 110, east longitude, to the sea (l. c., map 8); and, in addition, to a portion of the Siang Valley in Hunan Province, a tributary to the mid-Yangtze Valley.

In the twelve years that have elapsed since that work was compiled additional records have been obtained from various areas in the central and lower Yangtze basin, while an apparently separate endemic center has been located in a village near Shuichow, on the North River, above Canton (Vickers, 1920).

Methods of attacking the problem of the geographical distribution of schistosomiasis japonica.

Among other methods utilized to analyze more definitely the problem of distribution of the disease, schistosomiasis japonica, in the Orient, with particular reference to China, and with the hope of possibly locating new centers of the infection, we sent out questionnaires in the summer of 1922 to all doctors in central, southern and western China, asking for certain information bearing on the problem in China. This portion of the country covered all of the areas where the presence of the disease was considered at all possible, and, in addition, certain territory (that of Honan Province) north of this area, where the infection was not known to exist, but where, through a misunderstanding, certain textbooks have stated it to be present.

The questionnaire was divided into two parts, part 1 being preliminary and part 2 supplementary. Part 1 related to the presence of schistosomiasis in the vicinity of the hospital in which the doctor worked; if present, the approximate number of cases observed in the

past two years, the villages or region involved, the distance from the hospital, and the topography of the country where the infection was known to exist. In case no positive diagnosis of schistosomiasis had been made by microscopic examination of the stools of suspected individuals, inquiry was made regarding the existence of enlarged liver or spleen, or enlarged abdomen with ascites. The possibility of animals in the neighborhood harboring the infection, and the presence of any tradition among the natives that might aid in delimiting the infection was also suggested. Part 2 was to be used in case the area had diagnosed positive cases. It inquired more specifically into the patient's place of residence for the past four years, including his travels, his past history and family history, his clinical symptoms, ova found in his stools, and treatment administered.

Analysis of data.

In all, 222 questionnaires were mailed to clinicians, believed to be on the field. From this group 69 replies were received, or only 31 per cent. of those sent out. However, when allowances were made for duplication of personnel in the same hospital or for hospitals in the same city, and for doctors who were on leave, the number of returns was fairly up to expectation. Replies were received from sixty-five separate hospitals, representing sixty per cent. of the towns in the area where foreign hospitals were established.

The returns are summarized in Table I. They show that of the thirteen provinces to which questionnaires were sent, nine gave at least one positive report. Furthermore, inspection of the table reveals an important aspect of the problem, namely, that a greater proportion of the replies was returned from provinces with positive records than from provinces in which no cases had been known. A further inspection reveals the fact that the highest percentage of replies came from those areas from which the disease had been previously reported, namely, Anhwei, Chekiang, Hunan, Hupeh, Kiangsi and Kiangsu Provinces. However, our information provides sufficient ground for the belief that the questionnaire was successful, since it showed the disease to be present in two provinces not previously recorded to have cases, namely, Fukien and Szechuan. Likewise, four new centers of infection, in provinces previously known to have the disease, appeared in the replies. These are as follows: Taching, near Wenchow, in the southern part of the coast of Chekiang Province; Kityang and Kaying, in the northeast corner of Kwangtung, above Swatow; Jaochow, on the east side of Poyang Lake, Kiangsi Province; and

TABLE I.

Summary of questionnaires concerning schistosomiasis japonica in China.

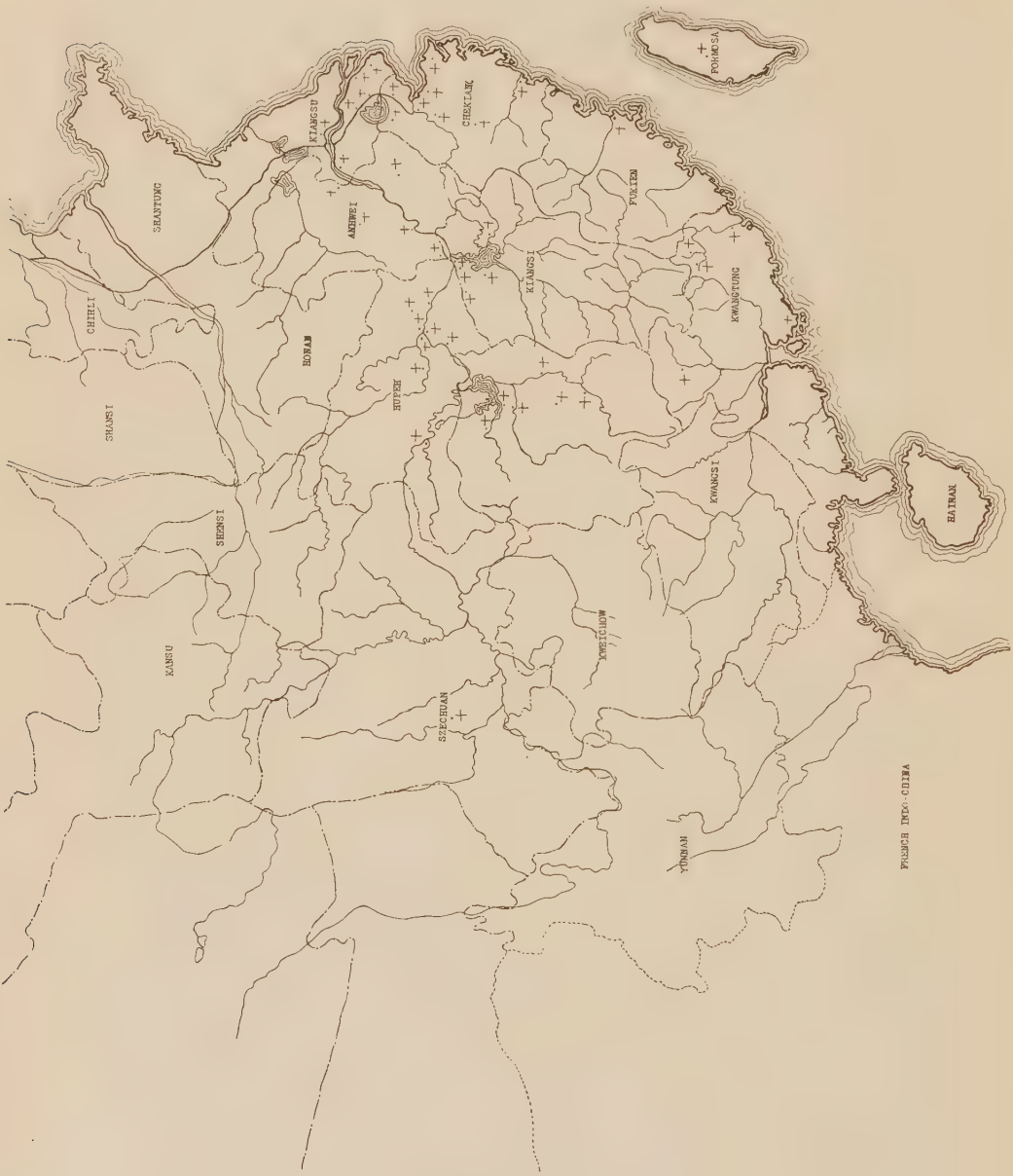
Province.	Questionnaires mailed.	Replies returned.	Hospitals represented.	Towns represented.	Positive replies.	New centers.
Anhwei.....	8	8	8	8	3	
Chekiang...	14	6	8	7	3	Taching
Fukien.....	25	5	25	18	1	Drongloh
Honan.....	16	3	15	14	0	
Hunan.....	16	7	13	13	4	
Hupeh.....	25	6	18	14	4	
Kiangsi.....	3	3	3	3	2	Jaochow
Kiangsu....	33	11	19	16	6	Liuho
Kwangsi....	4	2	3	2	0	
Kwangtung.	44	7	7	7	3	Kityang Kaying
Kweichow..	2	1	2	1	0	
Szechuan...	30	9	22	7	2	Jenshowhsien Junghsien (?)
Yünnan....	2	1	1	1	0	
Total.....	222	69	144	111	28	

Liuho, in central eastern Kiangsu Province. In addition to these data, the reports have made it possible for us to fill in gaps in the territorial extension of the infection.

Distribution of schistosomiasis in China.

From our study of the distribution of the disease, schistosomiasis japonica, from these and other sources, we have accumulated information, therefore, which permits us not only to add to the territory regarded as the endemic area in China, but to describe more exactly the boundaries of the endemic territory.

The general distribution of the disease in China is shown in map 2, which covers the endemic regions. The greatest area of endemicity is the Yangtze Valley, including not only the territory immediately watered by the main current, but also the adjacent lakes, particularly the Great Lake (Tai Hu) of Kiangsu-Chekiang Provinces, Poyang Lake in Kiangsi Province, and Tung Ting Lake in the Hunan area, as well as the important central Yangtze tributaries, the Siang and Han Rivers. Throughout the central and lower Yangtze Valley the



Map 2. General distribution of schistosomiasis japonica in China. + indicates a center of infection.

distribution constitutes practically one single extensive area. Above Hankow, in the main Valley, reports indicate its presence as far inland as Ichang, but above that region there is a stretch of about twelve hundred miles of river length for which no positive records have been made. Only in the upper portion of the river, in the central plains of Szechuan, where the south fork flows south from Chengtu, are positive reports of the infection made. This anomalous situation will receive special consideration later on. The amount of territory in which the disease is prevalent in the lower Yangtze Valley is, no doubt, increased by the presence of the Grand Canal, intersecting the Yangtze River at right angles, in the vicinity of Chinkiang, allowing a direct connection, both of distribution of the mollusc host and of the spread of the disease, by human intercourse.

Coastwise, schistosomiasis japonica is not known to be present in China, north of the mouth of the Yangtze River. South of the river it is now known to exist in several localities along the coast or in the coastal river basins. Thus Taching, in southern Chekiang, Foochow, Swatow and the country above Swatow on the Mei River, Hongkong and Shuichow on the North River all report positive cases, based on laboratory examination of the stools of suspected cases. On the other hand, the West River, above Canton, reports no authentic cases.*

The mountainous areas, embraced in the provinces of Kiangsi, Kweichow, and Yünnan, as well as those portions of the southeastern coastal provinces, lying above the coastal plain, report no cases.

In general, we may define the infected territory as one of abundant, slow-moving water courses, in which the river systems are supplemented by an abundance of fresh-water lakes, while these in turn are augmented by lesser streams, canals and irrigation ditches, all of which, in their turn, serve, at least during a part of the year, to supply water to the rice fields. One doctor in the field has referred to the endemic areas in his vicinity as a "lakeside district"; another clinician in an endemic center feels sure that the infected districts are confined to the regions of overflow at the times of heavy rainfall. While our evidence is not sufficiently detailed to make the sweeping statement that the entire stretch of country covered by the infection is at some time of the year an overflow area, such a statement is practically true for the central and lower Yangtze Valley, where the disease is of all places most extensive and intensive.

* The intermediate host, *Katayama nosophora*, has been found by us at Fatshan, in the Pearl River Delta, above Canton, making it altogether possible for the infection to become established there.

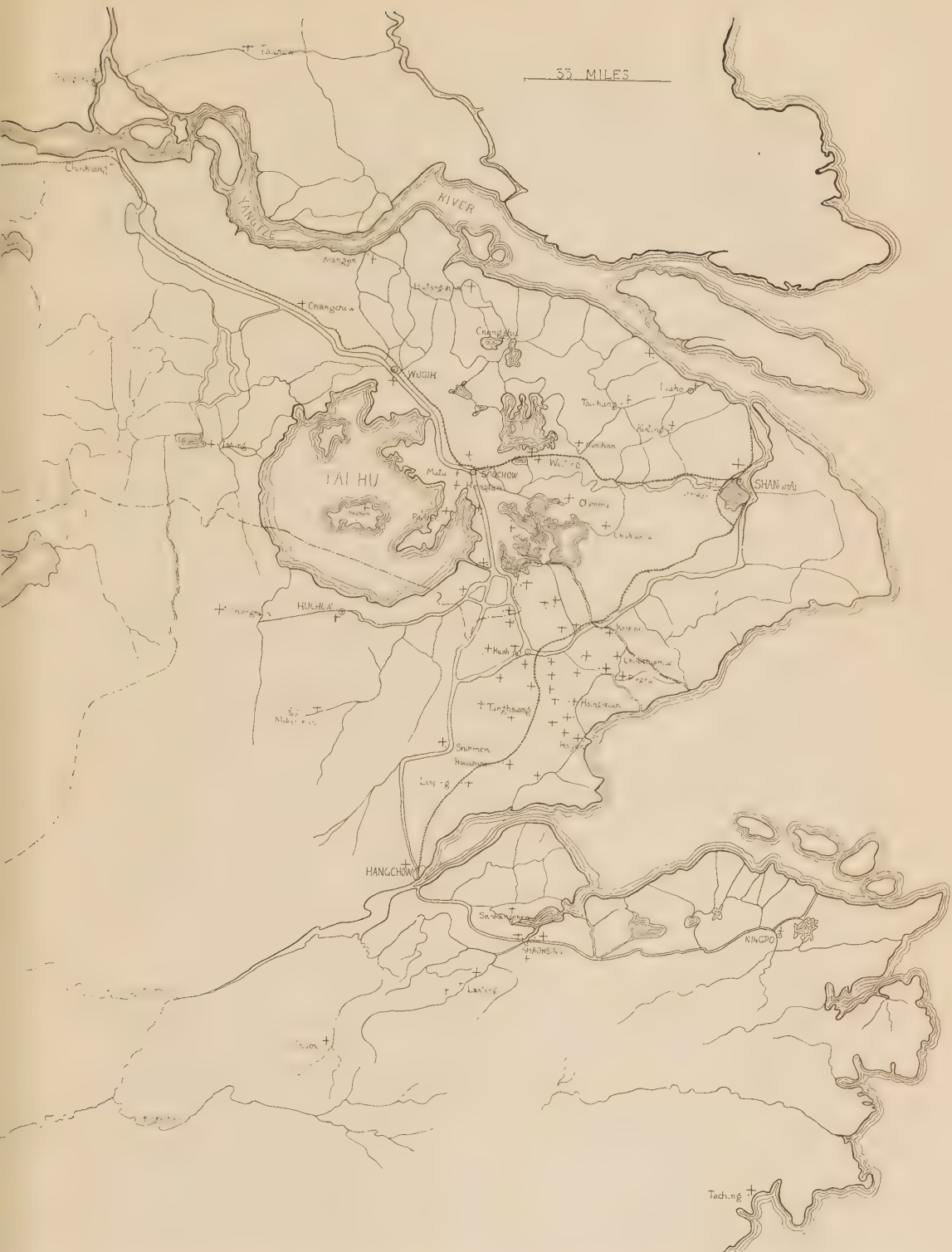
In order to observe the facts more closely in relation to the areas covered, it is our plan to present the data in our possession under two captions, namely, (A) those centers in which schistosomiasis japonica is now known to be endemic, to such an extent, as to constitute a really important factor in the life and economy of the population, and (B) those centers in which medical men have identified the infection among their patients, but have not recognized large numbers of cases of the disease. The former districts comprise six areas, (1) the Soochow-Kashing area, (2) the Wuhu area, (3) the Kiukiang area, (4) the Wuhan area, (5) the Siaokan-Tsaoshih area, and (6) the Yochow-Changteh area. This is in a sense an arbitrary division of the infected territory, since these areas are all contiguous, and since the hospitals in which the cases have been diagnosed were present before the disease was known to exist in China, and because the locations were considered to be strategic places for medical work. In spite of these facts, however, some of these hospitals have actually become prominent medical centers only since the discovery of schistosomiasis in their areas and, perhaps, because of the important rôle which schistosomiasis has assumed in their program.

(A) Areas of major infection.

(1) *The Soochow-Kashing area* (map 3). This area lies on the south side of the Lower Yangtze near its mouth. It may be defined more specifically as the region around the Great Lake (Tai Hu) and the country extending east of it to the sea. This territory is flat bottom land, comparable to a delta region. It is dotted with small lakes and is intersected at frequent intervals by canal systems. Cutting through it in a slightly northwest-southeast direction is the Grand Canal, which crosses the Yangtze at Chinkiang and runs down to Soochow, on the east shore of the Great Lake, thence south to Kashing and thence to Hangchow.

This area is an ideal one for rice growing. Water is available for irrigation practically the whole year round, and is led into the fields from primary canals through secondary and tertiary canals, and thence introduced by treadwheels up sluiceways into the rice fields, through which it passes in irrigation ditches. In no part of this area have we learned of the rice fields being lower than the canals. The towns and villages are situated on the banks of the canals. In large centers, like Soochow, the main canals run through the city and serve as traffic thoroughfares, taking the place of streets.

While the railroads between Shanghai and Nanking on the upper



MAP 3. Distribution of centers of schistosomiasis japonica in the region of the lower Yangtze River and the Great Lake (Tai Hu).

side of the area, and Shanghai and Hangchow on the lower side, pass through the heavy centers of endemicity, they are of secondary importance as local means of transportation, since the canal boats are the principal means of conveyance. Many families live on these boats through the entire year, travelling from place to place as trade and other conditions demand. This possibly explains why an important hospital, like the ones in Soochow in the center of the area, where a particular study of schistosomiasis has been made, reports cases from the northernmost part of the area, such as Yangchow, Chinkiang, Taichow, Changchow, Kiangyin and Hsitangshih, when hospitals nearer these centers, or in these very towns, which have not studied the problem carefully, report negative or only occasional cases of the disease from their vicinity.

While the most heavily infected region lies to the east of the Great Lake, in the region of the small lakes, east of Soochow, and in the network of canals down to and around Kashing, the endemic territory extends to the very gates of Shanghai, where it has been reported on the railroad at Chengju, just outside the city, and more nearly contiguous in a village near St. John's University. The fact that the intermediate molluscan host has been found infected in canals within the city of Soochow indicates that the infection is surely endemic within the walls of this city. Reports from the Kashing Hospital indicate that the infection is scattered over the whole territory, round about, without any one district being especially marked. This covers a radius of more than thirty miles, but is most pronounced to the east and north of the city.

The region lying to the southeast of Kashing, between Shanghai and the sea, gives no record of schistosomiasis. There is no hospital in this district, and it is not known whether the disease is present in this part of the area or not.

In the northern portion of the Soochow-Kashing area the infection has been reported from Yangchow, on the Grand Canal, and at Taichow, on a communicating canal to the east. Further down the River at Tsingkiangpu and at Nantungchow, both cities on the north bank of the River, reports from local hospitals are negative and no cases from these areas have been diagnosed in neighboring hospitals. Since no cases have ever been reported north of this region, it seems likely that these points lie just beyond the endemic region.

To the south of Kashing the infection extends to Hangchow, although the fewer number of cases reported from Hangchow would seem to indicate that the infection is not as severe in this locality, as

farther north. In the Chekiang peninsula, south of Hangchow Bay, local cases are known from Shaohsing, while foreign sport dogs in Ningpo are proverbially infected with the disease. Cases have been diagnosed at Wenchow and, inland, at Kinhwa. Patients suffering from the disease have been seen at the Shaohsing Hospital.

Reports indicate that infection with schistosomiasis is present along the south shore of the Great Lake and on adjacent canals, and that it extends up the west shore at least as far as Ishing.

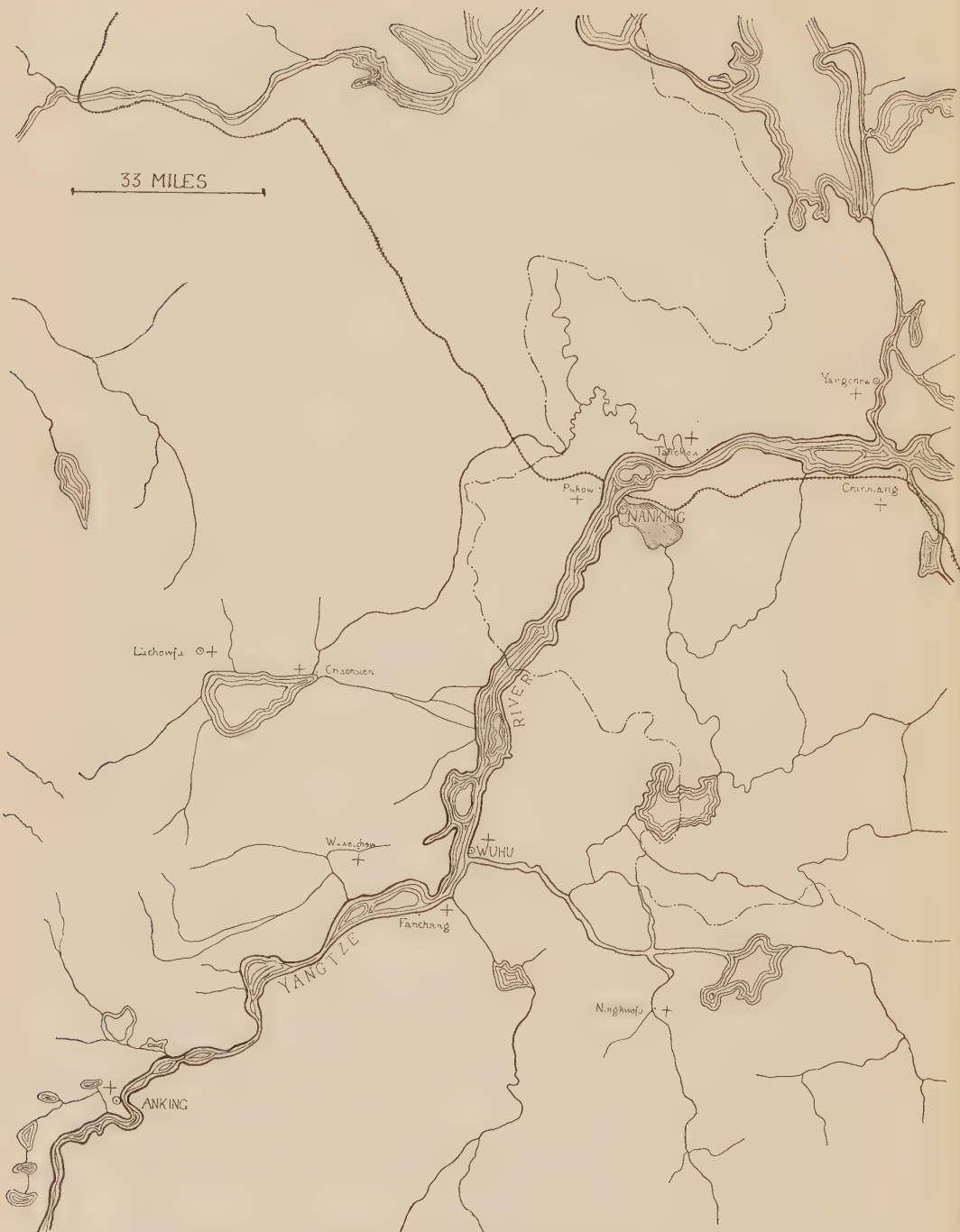
Present information provides a means for bounding the Soochow-Kashing area as follows. The main center of endemicity lies on the east side of the Great Lake, among the small lakes and canals near Soochow and Kashing. The Grand Canal which intersects this area is responsible for a narrow endemic strip from Yangchow above the Yangtze River to Hangchow on the south. The area as a whole is bounded by the Yangtze on the north, Shanghai on the east, and the mountains and hills to the south and west.

(2) *The Wuhu area* (map 4). This area was described by Houghton in 1910 in his report on splenomegalies in China. Wuhu is the focal point of the area. In general the endemic region lies among the backwaters of the Yangtze River, which flows through the area in a northeastern direction. It has seemed to us best to include Nanking and vicinity in this section and refer Susong, which lies in the southwestern part of Anhwei Province, to the Kiukiang area.

The vicinity of Wuhu is primarily a rice-growing region. Patients having schistosomiasis in the Wuhu Hospital come from towns which are well known for the rice produced in their vicinity. Wuweichow, somewhat down the River on the north bank, is a heavily infected center. Fanchang, on the south bank, and Ningkuofu, in the lake district to the southeast, are centers of infection. Lüchowfu has in the past been recorded as a center of infection, and Chaohsien is believed to harbor the disease (*fide* Houghton).

Nanking really represents a small region of infection, at present separated from the Wuhu region by about eighty miles of unreported territory. It seems likely that the infection is present also in the intermediate strip, but our present information allows us to make no definite statement concerning it. The Nanking sector joins the Chinkiang-Yangchow region on the west. All of the cases reported from here have come from the north side of the Yangtze, centering around Pukow. A few cases are on record from the country to the north, around Chuchow.

Up the Yangtze from Wuhu lies the Anking region of the area.



MAP 4. Distribution of center of schistosomiasis japonica in the Wuhu area. (This map joins map 3 on the west).

The country around Anking, back from the Yangtze, is one of small lakes with connecting water systems. Here, too, a large proportion of the schistosome cases are rice farmers.

The endemic regions of infection represented on map 4 are really confined to the back waters of the Yangtze, near its main course. The more remote points may be regarded as outlying centers of the infection, on a canal system centering at Wuhu and intersecting at right angles the main River.

The Wuhu area of schistosomiasis may be delimited as follows. On the east it is contiguous with the Soochow-Kashing area at the intersection of the Grand Canal and the Yangtze River; except at Nanking, the disease is endemic along the course of the River on both banks; it extends back from the River in certain places where there are intercommunicating canals. The northernmost points, where it is reported, are at Chuchow and Lüchowfu, where occasional cases are on record. The southernmost place on record is Ningkuofu. Whether the disease extends up the canals above Ningkuofu, or whether the endemic area is contiguous with the centers of infection on the west bank of the Great Lake remains to be determined.

Since the Wuhu area is one of the most heavily travelled thoroughfares of trade in China, patients with schistosomiasis are at times recorded in hospitals here from such remote centers as Kanchow, in southern Kiangsi Province, Changteh, on the west side of Tung Ting Lake in Hunan Province, and Ichang on the Yangtze River above Hankow. Such records give no indication where the individual was infected, since the waterways through which the patients come are all potential sources of infection.

(3) *The Kiukiang area* (map 5). This area is a center of very heavy infection, comparable to the Soochow-Kashing area. Topographically it consists of a wide river valley through which the Yangtze meanders, overflowing the entire region at times of high water, with steep mountain ranges rising abruptly out of the plain. The river bends to the south in a broad curve between Anking and Hankow, with Kiukiang at its southern tip. At this point, likewise, Poyang Lake with its extensive mountain tributaries meets the Yangtze River. With the waters of the River proper, that of the Lake, and subsidiary mountain torrents, all passing by this bend, Kiukiang is a natural center for determining the incidence of schistosomiasis in this area.

As a matter of fact Kiukiang actually constitutes a focal point of several very heavily infected districts. All points on both sides of

the River, within fifteen or sixteen miles of Kiukiang, have numerous cases of the disease, while the city itself has an infected section at South Gate Lake. Furthermore, the west side of Poyang Lake, between the shore and the Kiukiang-Nanchang railroad, is heavily infected. Case reports come from all along this rail line, extending to the west as far as Yüchiahu. As yet no information has been received from Nanchang, although the delta country between Nanchang and Poyang Lake seems to be a suitable location for the infection.

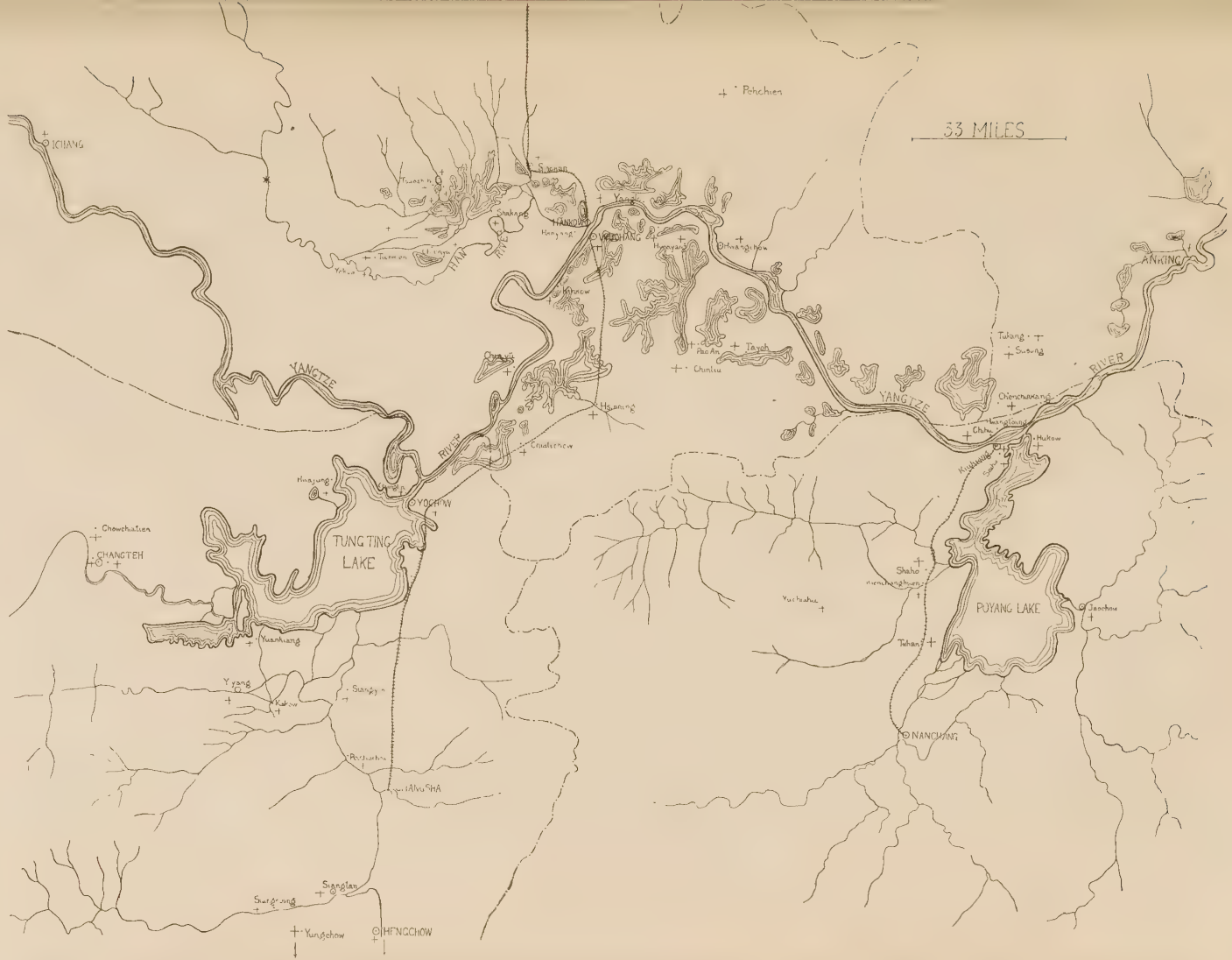
On the east side of the Lake, Hukow, across from Kiukiang, harbors the infection. In the low, rice-growing country around Jaochow the disease is again commonly found. The intermediate country on the east side of the Lake consists of higher ground, where beans, wheat and tobacco are grown. This elevated region is definitely reported not to harbor the disease.

There is little information in hand regarding the possible presence of the disease to the south of Poyang Lake, up the river from Nanchang. A patient from Kanchow, in a district south of Nanchang, beyond the area covered by map 5, has been diagnosed as a sufferer from the infection in the Nanking Hospital, but it was impossible to determine the source of his infection, since he was a boatman, and had made the trip from Kanchow down the river to Poyang Lake, thence through the Lake to the Yangtze River, and down the Yangtze to Nanking once each year, and could have incurred the infection at any place along his long water trip.

Cases from Susong and Tukang frequently report to Kiukiang for treatment of the disease, although they likewise travel downstream to Anking and Wuhu for medical attention.

The Kiukiang area for schistosomiasis is adjacent to the Wuhu area in the region of Susong. On the north side of the River it is confined to the backwaters which, at times of overflow, cover the entire broad valley. On the east side of Poyang Lake the infection is fairly well distributed, except in the high ground between Hukow and Jaochow. The topography at the south end of the Lake and southward up the river valley is such as to warrant the belief that schistosomiasis exists there, but no definite data have been obtained. The infection is common along the entire west shore of the Lake, and possibly up the river systems flowing into the west side of the Lake, but further west it is intercepted by the high mountain ranges.

(4) *The Wuhan area* (map 5). This area is one where the Yangtze River holds fairly well to its banks, but where the backwater is impounded in lakes of various sizes. The endemic centers of schisto-



Map 5. Distribution of centers of schistosomiasis japonica in the Central Yangtze Valley, including the Kuikiang, Wuhan, Siaokan-Tshaoshih and Yochow-Changteh areas. (This map joins map 4 on the west).

somiasis japonica in this region are found almost exclusively among farmers and boatmen in villages along the shore or near the region of these lakes, while the Yangtze River flows through the area, carrying off the excess of water and serving as an artery of commerce.

Although the foci of this area naturally center at Wuchang-Hankow, the district of greatest infection lies in the lake region on the south side of the River, extending practically to the south boundary of the Province of Hupeh. The easternmost town in this region reporting cases is Tayeh, but there is no known reason why the disease does not extend down the River Valley, all the way to Kiukiang. From Tayeh west, southwest and northwest the country is heavily infected. The towns and villages on the map indicate only partially the extent of the disease in this district.

Yet the infected region is not confined to the south of the Yangtze River, for cases from Hwangchow, Yanglo and even Pehchien confirm the presence of the infection on the north side of the River. Likewise, Hanyang and Chiayü prove that it is found on the west side of the River.

The area is intersected on the north by the Peking-Hankow railroad and on the south by the Wuchang-Changsha railroad, the latter rail line running through a heavily infected district between Hsinning and Chialichow.

While Ichang lies outside of this area, for convenience it may be considered in this section. Local hospitals in Ichang return negative reports on schistosomiasis from that region, but there are definite records from Hankow of patients from Ichang harboring the infection. Furthermore, the account of Mann (1916) indicates that American sailors incurred the infection while bathing in tributaries of the Yangtze River just above Ichang, while one of Thompson's patients in Hankow (1911) contracted the disease in that locality.

The Wuhan area is continuous on the east with the Kiukiang area, at the point where the Yangtze River flows over the Hupeh-Kiangsi Province boundary. It is bounded by a line drawn southwest from Tayeh to Yochow, thence north to Hankow, thence north to Pehchien, thence southeast to the Yangtze River. Practically this entire area is covered with the infection.

(5) *The Siaokan-Tsaoshih area* (map 5). This is a comparatively small area, but is well defined and is heavily infected. It consists of the lower Han River Valley, above Hankow, and the lake region immediately to the north of it, which constitutes a flood reservoir of the Han and the Yangtze Rivers. This overflow extends up the

Han River about 150 miles above Hankow, to a point indicated by the star (*) in map 5. The region of infection is a lakeside district. The water drains into the lakes from the higher lands to the north, and after passing through the lakes flows out through several channels into the Han River. A glance at this area on map 5, which has been prepared for us by Dr. J. Lee H. Patterson of Tsaoshih, shows the general distribution of villages from which the infected cases have been diagnosed. The river lands are relatively free from the infection, while the villages about the lakes are heavily endemic for the disease. The country south of Siaokan, as far as Hankow, is covered with endemic spots, but by far the most heavily infected region is located south of Tsaoshih, in the counties of Hanchuan, T'ienmen, and Yingcheng. All of the rice field districts to the north, east, and west of Tsaoshih are known to be sources of infection. In Tsaoshih, a country market town, about one hundred and fifty cases of the disease are diagnosed each year, and this necessarily constitutes only a very small fraction of the population harboring the disease.

While most of the patients infected with schistosomiasis japonica, within the Siaokan-Tsaoshih area, report either to Siaokan or Tsaoshih for diagnosis and treatment, some cases from this district are seen at Hankow. It seems reasonably certain that the disease does not occur north of this lake district, since careful investigations in northern Hupeh Province at Siangyangfu and at Fanchang have never brought to light a single case of the disease. On statistical grounds, the infection can be ruled out of northern Hupeh and from the Province of Honan still farther to the north. Statements to the contrary, which have gotten into textbooks on tropical medicine, are based on inadequate information.

The infected area in this district is well defined. It extends from Hankow, on the east, for about one hundred fifty miles up the Han River Valley. On the north it extends very little, if at all, beyond the lake area between Siaokan and Tsaoshih. It is not known in the district south of the Han River, between the Han and Yangtze Rivers.

(6) *The Changteh-Yochow area* (map 5). This area lies wholly within the northern part of Hunan Province and is adjacent to the part of the Wuhan area along the south bend of the Yangtze River, where the waters of Tung Ting Lake flow into it. It consists of all the country immediately surrounding Tung Ting Lake and the overflow land of small lakes and canals flowing into the Lake.

On the north the region around Hwajung is heavily infected, while Laning (1914) believed that some of his men contracted the infection

at Changlin, near the mouth of Tung Ting Lake, across from Yochow. The country around Yochow is heavily infected. More specific inquiry needs to be made as to the exact extent of the infection in this district, since Laning (l. c.) thought the disease might have been contracted from the waters of the Lake itself, although he furnished no positive evidence to support his hypothesis.

On the west side of the Lake the infection is probably confined to the vicinity of Changteh City and the surrounding districts in Changteh County. This region has been the subject of a recent investigation by Dr. George Tootell, who found that, aside from Changteh City, the infection in the immediate neighborhood was particularly severe in the villages of Tukow and Chowchiatien.

South of the Lake the disease is confined not so much to the immediate shore of the Lake as to the region of interlacing canals and small lakes, particularly between Yuankiang and Yiyang, from which section numerous cases have been reported. There are, however, spots of infection up the Siang River Valley, even as far as Changsha, Siangtan and vicinity. On the southeast at Pingkiang, no cases have been observed.

Lying considerably to the south, beyond this endemic area, is the South Hunan region of schistosomiasis. The reports from Hengchow indicate that the actual region of infection lies above Yungchow, near the village of Peishui. Cases from this area were originally reported by Peake (1909). Several cases a year from this region come to the Hengchow Hospital for treatment.

The Changteh-Yochow area is bounded by the Yochow sector on the east, and the Changteh sector on the west. On the north, the disease is prevalent in and around Hwajung, and on the south of Tung Ting Lake it extends into the overflow region of lakes and canals, where at Yiyang, Yuankiang, Kiakow and vicinity it is frequently found, while at Changsha it is less common. In the upper waters of the Siang River, near Peishui, it has also been reported.

The infective incidence of schistosomiasis japonica in the major endemic areas.

Until more specific epidemiological surveys are made in infected areas the actual incidence of infection of schistosomiasis japonica in China and other parts of the Far East will remain a mere guess. In hospital centers, caring for large numbers of schistosome cases, the incidence of clinical cases each year in their vicinity is estimated as follows:

1. *Soochow-Kashing area.* (*a*) Soochow Hospital. Five per cent. of the farming and village population east of the Great Lake. In some villages 95 per cent. of the inhabitants are infected.

(*b*) Kashing Hospital. Seven and a half per cent. of the farmers and coolie class, including wives and children. In some villages the incidence of schistosomiasis japonica among the village population is probably more than fifty per cent.

2. *Wuhu area.* Laning (1914: 20) quotes Houghton, as stating, that in this area "thousands die yearly of this disease, with other thousands incapacitated by it." (Doctor Houghton believes this estimate will be borne out by statistical study.)

3. *Kiukiang area.* Exact information is not at hand. Perhaps five per cent. of all the farmers and boatmen in the vicinity of Kiukiang have clinical schistosomiasis.

4. *Wuhan area.* In the Church General Hospital, Wuchang, 2.64 per cent. of the medical cases in the hospital have schistosomiasis. The percentage is certainly far higher in local centers of infection.

5. *Siaokan-Tsaoshih area.* (a) The London Mission Hospital, Tsaoshih, reports one hundred and fifty clinical and laboratory cases a year.

(b) The London Mission Hospital, Siaokan, reports forty clinical and laboratory cases a year. Probably forty per cent. or more of the village population along the lakesides harbor the infection.

6. *Changteh-Yochow area.* The Changteh Hospital reports ninety-three per cent. of the males and seven per cent. of the females examined in an epidemiological study of two infected districts (Tukow and Chowchiatien). Only one or two per cent. of the medical cases in the hospital suffer with schistosomiasis.

Inspection of these data indicates very meager information, indeed, when one considers the population of the endemic areas at large. Even if hospital cases were considered on a statistical basis, they are subject to the criticism that they represent only the sick population. But in China the greater part of the natives visit the foreign hospital only as a last resort, while superstition and prejudice keep many of the serious cases at home.

(B) Areas of minor infection.

Outside of the six areas, just described as being important endemic districts of schistosomiasis japonica, the following centers have been discovered.

1. *The Szechuan area.* This is apparently a small district in

the middle Szechuan plain, south of Chengtu, at Jenshowhsien, and possibly also at Junghsien. In the former locality several cases have been reported. The region is on a tributary of the south fork of the Yangtze River, at an elevation of from six to eight hundred feet on the plain, while high mountain ranges lie to the south and west. The infection lies in a rice-growing district, where the hills are terraced and watered from mountain streams. Aside from these meager data we have no information. All other sections of Szechuan report negative findings.

2. *The Fukien area.* The only local record for the Province of Fukien comes from Drongloh, across from Pagoda Anchorage below Foochow. This is a low delta region near the sea, well supplied with canals and given over to rice-growing. The infection seems not to be confined to the farming class alone, for Fukienese boatmen in Singapore are known to harbor the infection (autopsy findings).

3. *The Swatow area.* A single local case is reported from the Han River north of Swatow, at Chaoyanghsien. Other cases have been reported at Changloh and Pyangtshun, from the rice fields of this district, but the diagnosis needs confirmation. Swatow boatmen in Singapore are known to harbor the infection (autopsy findings).

4. *The North River area.* This infection was reported by Vickers in 1920. The infected region is in and around the village of Cheung Shu Ta'am, a small hamlet not far from Shuichow, on the Canton-Hankow railroad. The water supply of this district comes from mountain streams. Three or more cases have been positively diagnosed from this area.

Summary of the endemic regions in China.

A careful study of the information in hand indicates that by far the greatest part of the territory infected with schistosomiasis in China is the Yangtze Valley flood area. *The main course of the stream is not known to be responsible for a single case of infection of schistosomiasis japonica, and the biological evidence on the habits of the molluscan host argues in favor of this view.* However, all of that area which lies in the bottom land of the Yangtze basin, intermediate between the source streams and the mighty River, constitutes a reservoir of water, which in time of flood not only receives the flow from the Yangtze tributaries but also the backwater of the Yangtze itself. Thus, in the wet season, this whole area is frequently inundated, while in the dry season it is resolved into lakes, swamps, marshes and alluvial bottom land. The rich silt land is easily watered during the rice-growing season by

natural or artificial canals, which usually have their source of supply in the backwaters rather than in the Yangtze River.

The other areas outside the Yangtze Valley where the infection exists are in narrow valleys, where the rice fields are usually terraced and supplied with water from mountain streams.

It is possible for us, with the present information in our possession, to describe quite accurately the large endemic areas of schistosomiasis japonica in China, both on the basis of distribution of clinical cases and (*a priori*) on the basis of topography of the territory where it is possible for the infection to occur. Beginning at the Yangtze River mouth it is confined to the south bank of the River, until the River is intersected by the Grand Canal. Here the endemic territory extends north to Yangchow and Taichow, thence across the Province line to Anhwei Province, where the northern limit of the infection is bounded by a line drawn from Chuchow to Lüchowfu. At this point the endemic region bends south to the Susong sector, following the course of the Yangtze; thence to Peichien, Siaokan, Tsaoshih and to the limit of overflow of the Han River, one hundred and fifty miles above Hankow.

The region south of the Yangtze River is less easily bounded. A heavy infection lies south of the River, but becomes less and less important as one leaves the overflow areas immediately adjacent to the Yangtze. The southern limit of the infection is extended considerably by the three large lakes, Tung Ting, Poyang, and Great Lake, centers around which heavy infections exist. In the case of each of these lakes the main water supply comes from one or more extensive river systems leading down from mountain streams. The infection exists far up near the source of Tung Ting Lake. The same may be true for Poyang Lake, although this point has not been verified. In the Great Lake area the infection has not been traced above Ishing, on the west, or Kinhwafu, on the south. Changteh, on the west, and Shanghai, on the east, mark the west and east boundaries of the infection on the south bank of the Yangtze River.

The long stretch of the Yangtze River gorges, above Ichang, is not a place for backwater of the River to accumulate. This may explain why no cases have heretofore been reported from the Yangtze basin above Ichang. On the other hand, one must keep in mind the possibility that the district of sandstone through which the Yangtze River cuts in eastern Szechuan Province may make it impossible for the molluscan host to develop in this territory.

The endemic infections in Fukien and Kwangtung Provinces are as yet little known, making it impossible to delimit them until more specific information is available.

Comparison of the Chinese and Japanese areas endemic for schistosomiasis.

At first thought a comparison of the endemic centers of schistosomiasis japonica in Japan and in China (see maps 1 and 2) would seem to indicate that the distribution of the disease, as determined by the topography of the two countries, is entirely different. China is a broad expanse of the Asiatic Continent; Japan is an island country. China has long river courses; Japan has short coastal rivers. Yet a more careful study reveals many points of similarity. If one considers the Yangtze River to be a very deep inlet of the sea, containing fresh water throughout the greater part of its course, because of the abundant supply from its tributaries, and because the sea itself is too far distant for the tide to materially affect it, then the areas of endemicity in China are more readily comparable to the Japanese areas. Furthermore the comparison is facilitated by the fact that the Yangtze River itself is not the source of schistosomiasis, and that the endemic centers are in the lake and canal and other tributary systems, back from the main stream.

Although the Japanese rivers are relatively short, compared with the Yangtze, they are comparable to the coastal streams of Fukien and North Kwangtung Provinces, where we have shown the disease to be present. Furthermore, the Tone River in Japan extends across the main island for a considerable distance. Except for the Numazu area, the infected districts in Japan, although near the sea, really constitute overflow areas. Thus the Katayama district, around Fukuyama, has many points of resemblance to certain topographic features of the Wuhan area, while the Tone River district is not unlike the lake region in the Siaokan-Tsaoshih area. The main difference in each case is this, that the Chinese districts of infection are far more extensive than the Japanese districts, while the Japanese areas are, by natural conditioning circumstances, usually intensive centers of infection. In other words, the Japanese areas are miniature replicas of the Chinese areas. We are not in a position to make accurate estimates of the relative difference of extent of the infection in the two countries, but it seems not unreasonable to estimate that all of the five known Japanese endemic areas can be superimposed on any one of the large endemic regions in China, and leave considerable infected territory around the margin of that area. To consider the extent of the territory in China as ten-fold that in all of the Japanese districts seems well within the limits of probability.

The next point that naturally arises is the relative incidence of the disease in the two infected populations. Baelz's original survey of the Katayama district (1883) recorded an infective incidence of twenty per cent. among the population. Kobayashi found the infection in the Tone River district to vary between seven and thirty-six per cent. These figures are considerably above the estimates made for the population of the infected districts of China as a whole, where seven per cent. is the highest reckoning made. It must be kept in mind, however, that districts, estimated in China, cover considerably more territory than they do in Japan, and where villages in infected areas in China have been surveyed the percentage of population infected with the disease has been surprisingly high. Dr. Tootell's recent survey of villages in the Changteh area, where in Chowchiatien ninety-five per cent. of the males examined were infected, and in Tukow, where eighty-seven and a half per cent. of the males were infected, supports this view. Certain villages in the vicinity of Soochow show an infective incidence of from fifty to ninety-five per cent.

The reservoir hosts of schistosomiasis as related to the distribution of the disease.

In Japan domestic and wild animals are important factors in the perpetuation of schistosomiasis in endemic centers. Dogs, cats, oxen and horses are all known to harbor the infection in nature. Many laboratory animals have been found susceptible to experimental infection. In the Katayama district field mice are described as important reservoir carriers of the disease. In Formosa, the infection is described from domestic animals, including cattle, oxen, dogs and hogs. Since the problem in the Philippines has never been studied by investigators working in the endemic centers, no data are available on mammals harboring the infection in those islands.

In China a few definite data are at hand. In practically all localities where the disease exists, foreign hunting dogs have become infected, have developed a typical schistosomiasis dysentery, and because of their economic value, laboratory examinations of their feces have been made. The areas from which foreign dogs are reported, as susceptible to the disease, stretch from Shanghai and Ningpo to Chungking. While Chinese native dogs are at times found infected, their dislike for the water probably explains the low incidence of infection among them. We have seen the disease in a native dog at Kiukiang and at Shaohsing. Doctor F. P. Manget of Huchow, Chekiang Province, reports that laboratory examinations of sheep,

cats and pigs are negative. Doctor C. McA. Wassell states that cats are infected in Wuchang. He has autopsied dogs with acute schistosome infections. Doctor C. F. Wills, of Siaokan, Hupeh Province, writes that dogs and imported cattle are infected, but that native oxen are immune. Horses are not used in the endemic areas and donkeys are rare. Field mice have not been examined in endemic centers in China.

The heavy infection within certain circumscribed areas in Japan, in contrast to the estimate of light incidence of the disease over extensive areas in China, may be based on this fact, that there are more animals in Japan serving as reservoir hosts, conserving the infection and seriously supplementing man as the definitive host, whereas in endemic centers in China native domestic work animals are fewer, both as to kind and as to actual numbers, and of these the water buffalo is apparently immune. Native dogs in China, by their habits, are less subject to infection than the dogs of Japan. In other words, *in China man alone is the important definitive host.*

The spread of schistosomiasis.

Until the exact distribution of the disease is known throughout all parts of the endemic territory in China it is futile to attempt surveys to determine whether the disease is increasing or decreasing in China. Observations have been made in Japan (Mizobuchi, 1915), showing that in the Tone River district schistosomiasis has been spreading of recent years. Doctor H. Kobayashi, in a private communication to us, states that in Saitama prefecture near the Ara River, the snail, *Katayama nosophora*, occurs, whereas the disease is not known to occur. "I am convinced," he continues, "that the disease will be found to be present, when the study of the subject has been carried on in that district." Recently uninfected *Katayama nosophora* have been found by us in South China in an area where no cases of schistosomiasis have been observed. Moreover, this warning can be definitely vouchsafed: that wherever the intermediate host of schistosomiasis lives, even if it is not now infected, a real danger of future human infection exists. The solution to the problem demands, first of all, the identification of all snails which can act as intermediate hosts. Next, the distribution of these snails must be mapped out. In the third place, an epidemiological survey of all such territory must be undertaken to determine in how far the distribution of the molluscan host corresponds to the present distribution of the disease.

ACKNOWLEDGMENT.

To all the physicians in China who were kind enough to provide us with the information contributory to the analysis of the distribution of schistosomiasis japonica in China we wish to express our most sincere thanks.

SUMMARY.

1. This study was undertaken to analyze more definitely the distribution of schistosomiasis japonica in the Orient, more particularly in China, with the hope of delimiting the known endemic areas and locating centers not yet on record.

2. In addition to the accumulated information on the distribution of the disease for the past decade, considerable new data were obtained, partly through questionnaires sent to doctors in central and southern China, which inquired into the presence of the disease in the vicinity of the hospital in which the doctor worked; if present, the approximate number of cases observed in the past two years, the villages or region involved, and distance from the hospital and the topography of the country where the infection was known to exist. Inquiry was also made into the clinical symptoms observed, reservoir hosts of the infection, and traditions of the natives that might help in recognizing the infection.

3. Of the thirteen provinces in China where schistosomiasis japonica might be suspected to exist, nine have one or more definite areas of infection. Two of these provinces, Fukien and Szechuan, have not been previously recorded as harboring the infection.

4. The main territory of infection is in the Yangtze basin. For purposes of convenience we have divided it into six major areas of infection, which are referred to as (1) the Soochow-Kashing area, (2) the Wuhu area, (3) the Kiukiang area, (4) the Wuhan area, (5) the Siaokan-Tsaoshih area, and (6) the Changteh-Yochow area. These areas constitute practically one continuous stretch of infected country from the sea up to Ichang.

5. Schistosomiasis japonica is not associated with the main current of the Yangtze River, but is found in the overflow areas and backwaters of the Yangtze basin, particularly in the region of lakes and canals adjacent to the River, where clear, quiet water is found. For this reason most of the endemic centers are found south of the River, particularly in the region of the three large lakes, the Great Lake, Poyang Lake and Tung Ting Lake, their tributaries, and intermediate lesser lakes, swamps and marshes. The Siaokan-Tsaoshih area

occupies a similar situation among the small lakes on the north side of the Han River above Hankow.

6. In these major centers of endemicity the percentage of infection among the country population ranges from one to seven per cent., although in some heavily infected villages, where surveys have been made, the disease may affect as high as ninety-five per cent. of the population.

7. In addition to the Yangtze basin between Ichang and the sea, the following lesser areas of infection are known:

(*a*) The Szechuan area, where several cases have been observed at Jenshowhsien.
(*b*) The Fukien area, where an infection exists at Drongloh.
(*c*) The Swatow area, where the disease has been recognized on the Han River above Swatow.
(*d*) The North River area, where cases from the region of Shuichow have been observed.

8. A comparison of the areas of endemicity of schistosomiasis japonica in Japan and China reveals the following facts. If the Yangtze basin is considered as an inlet of the sea, then the endemic areas in both countries are comparable as regards topography, except that the Japanese areas are only miniature replicas of the Chinese endemic territory. All five of the Japanese areas could be superimposed on any one of the larger endemic areas in China and leave a considerable portion uncovered. It seems not improbable that the infected areas in China cover ten times as much territory as the Japanese districts of infection.

9. On the other hand, much of the Chinese territory is probably less heavily infected than the Japanese areas. For in China heavily infected villages are separated by less heavily infected country. The condition in China is partly due, no doubt, to the smaller number of reservoir hosts exposed to the infection in China, resulting in a diminution of the underlying infective incidence among the molluscan hosts, and a consequent lessening of the danger to man.

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VI. THE PATHOLOGICAL ANATOMY OF THE DISEASE.

(Plates XXII to XXXI.)

The pathology of infection by *Schistosoma japonicum* was recognized long before the nature of the parasite itself was known. The earliest record of the disease was made by Fujii (1847), when the disease became known as "Katayama disease" from the name of the district in Japan where it was described. The first mention of the disease, in a language other than Japanese, was by Baelz (1883) working in Japan, who described the clinical features of schistosomiasis, but attributed them to infection with *Clonorchis sinensis*, which he found in the livers of some of his patients. Yamagiwa (1890) described a case of Jacksonian epilepsy in which ova were found in the brain. At that time he attributed his findings to infection by the lung fluke, *Paragonimus westermani*, but later identified the ova in his sections as those of *Schistosoma japonicum* (Fujinami, Tsuchiya and Miyagawa, 1916). At about this time, the Japanese became keenly interested in the Katayama disease, and many investigators described the pathological findings in typical cases coming to necropsy. This work, however, was all published in the Japanese language, and it was not until Katsurada (1904) published in German his description of the parasite and of the pathology which it produced that knowledge of the disease became general.

With the experimental infection of animals the pathology of the early stages of the disease, especially that of the period of invasion, was studied by the Japanese, thus completing in general the pathological picture.

There are, however, several details in the biological activity of the parasite, and in the development of the lesions produced, concerning which there has been disagreement among investigators; and there are other points which have not been satisfactorily explained. The Japanese, for instance, are still in disagreement as to whether there is a skin eruption associated with the penetration of the cercaria into the skin, and if so, whether the eruption is the disease called "Kabure" in Japan, which attacks farmers after wading in the water of the rice fields. Another point, very difficult to establish, is the exact mechanism by which the worm succeeds in depositing its eggs in the wall of the intestine, and what the main factors are which are responsible for

the escape of the eggs into the lumen of the intestine. Again, the formation of papillomata in the mucosa of the colon is one of the prominent features of late stages of the disease, but the method of formation of these papillomata has not been thoroughly studied.

It is our purpose to review the various stages of the pathology of the disease, and to pay particular attention to the features which have heretofore not been sufficiently emphasized. It is convenient to divide the pathology of schistosomiasis japonica into the following stages:

I. The stage of invasion and maturation of the parasite.
II. The stage of egg deposition and extrusion.
III. The stage of tissue proliferation and repair.

Material for study.

Our observations are based upon the study of necropsy material from three human cases of schistosomiasis japonica, and of tissues from forty mice, thirty rabbits and thirty-six dogs infected in our own laboratory. Our material from human cases is too small in amount to warrant generalizations from it alone, but since it shows only the lesions of the later stages of the disease, which have been presented already by many writers, we shall emphasize more the early pathology, as shown in animals, and conform to the previous descriptions of human lesions, except where our observations seem to add new information.

The microscopic sections were prepared from blocks of tissue fixed either in 10 per cent. formalin or in Zenker's solution. All tissues were imbedded in paraffin. Routine and serial sections were stained with hematoxylin and eosin, and other special sections with Giemsa's stain for eosinophile differentiation. Serial sections of the following tissues were cut at 10 micra: the torso of one mouse, killed twenty-four hours after immersion in infected water; a piece of skin from one dog, fifteen hours after infection; a lobe of lung and of liver and the whole diaphragm of four mice, from four to seven days after immersion; a part of one kidney of a rabbit, four days after immersion; a piece of lung from a dog, fourteen days after immersion; and many blocks of intestine from dogs, twenty-five to sixty days after infection.

I. The stage of invasion and maturation of the parasite.

A. The lesions produced by skin penetration.

The pathology produced by the penetration into the skin of such a minute organism as the cercaria of *Schistosoma japonicum* is slight, but

nevertheless is important in connection with the biology of the parasite. The apparent insignificance of the reaction is responsible for the fact that infected patients are often not aware of any lesion at the time of infection. Furthermore, especially in Japan, there has been disagreement among investigators as to whether the infection is associated with a definite dermatitis, and many experiments, both human and animal, have been performed for the purpose of settling the point. The dermatitis, known in Japan as "Kabure," was considered for several years to be produced by the penetration of this parasite into the skin. This dermatitis Miyagawa (1913) describes as red, flea-bite-like, lentil-sized papules appearing two to three days after immersion in rice-field water. The appearance of the lesions is preceded by itching of the skin, and scratching brings out the lesions. These become smaller after four or five days, the redness disappears, and the itching is diminished. Miyagawa found no cercariae in sections of these lesions taken from an infected individual. He and his assistant, furthermore, experienced this skin eruption after immersion of their arms in rice-field water, but neither of them developed schistosomiasis. His servant, on the other hand, who went frequently into infected water, did not develop the dermatitis, but later showed ova of *Schistosoma japonicum* in his feces. Miyagawa also found that the "Kabure" dermatitis occurred in districts where schistosomiasis was not endemic. These observations seem to indicate that the "Kabure" dermatitis of Japan is not the lesion of penetration of the schistosome cercaria. It should also be pointed out that in China no such skin disease is known among the rice-farmers, in regions endemic for schistosomiasis. Neither was such an eruption seen by Laning (1914) in the closely observed cases of schistosomiasis on an American gunboat on the Yangtze River.

These negative findings do not mean, however, that no demonstrable skin lesion is produced by the penetration of the cercaria. Although Miyagawa (1913) failed to find any cellular reaction about the cercariae in the skin of his experimental animals, other observers, including Narabayashi (1916) and Sueyasu (1920), found hemorrhage and cellular infiltration about cercariae in the skin of infected mice. Nakamoto* placed cercariae on the skin of his forearm and soon afterward experienced intense itching at this point. After two hours' observation, however, he observed no macroscopic lesion. At the end of that time he excised the area of skin, and found cercariae among the cells of the epidermis, and in the superficial portion of the

* Personal communication.

corium, but without any cellular reaction of the tissue. In this case the duration of the experiment was probably too short for any tissue reaction.

Our observations lead us to conclude that there is a definite skin eruption associated with the penetration of the cercaria. We removed all the hair from the trunk and upper portions of the limbs of a young dog. The only lesions of the skin then visible were a few scattered red acneform papules, about a millimeter in diameter. We immersed this dog for one hour in water, heavily infected with cercariae of *Schistosoma japonicum*. Immediately after removal from the water the dog began licking his paws and lower legs vigorously, and chewed at them, as if searching for fleas. His attention soon changed to the depilated portions of his legs, which he licked vigorously. Ten minutes after removal from the water, and one hour later, he was carefully examined for macroscopic skin lesions, but none were found. The next morning, however, fifteen hours after infection, innumerable red, slightly raised, pin-point-sized spots were seen over all portions of the body which had been immersed in water. The anterior half of the chest and most of the back, which had not been immersed, were free from these lesions. The redness could be obliterated by pressure. Two pieces of skin were excised, each containing two macroscopic lesions. In the serial sections of these pieces of skin we found four cercariae, two in each block of tissue. All the cercariae were in the corium and three of them were surrounded by a definite tissue reaction, extending for about 0.2 mm. laterally in all directions, and slightly into the deeper tissues. The reaction consisted of edema, a moderately dense accumulation of wandering cells, and congestion of neighboring capillaries (Figs. 1 and 2). The wandering cells were about equally mononuclear and polymorphonuclear, and of the latter, about half were eosinophiles. In the congested capillaries polymorphonuclear leucocytes often crowded closely together along the walls. There was no hemorrhage into the tissues. The cercaria about which there was no reaction was close to the epidermis and may not have been in the corium long enough to have produced a reaction.

Further observation of this dog showed that the lesions became slightly more prominent up to thirty-six hours following infection, after which they faded. They were no longer visible eighty-four hours after infection.

One white mouse was treated in the same manner as this dog, but no visible skin lesions appeared, although the mouse later proved to be heavily infected with adult worms. Another white mouse was killed

twenty-four hours after immersion in infected water, and serial sections were made of its whole trunk. Many cercariae were found in the corium of the skin and in the subcutaneous connective tissue and fat. A few polymorphonuclear leucocytes were found in the tissue about some of these cercariae, but others, especially in the looser tissue, were associated with no visible tissue reaction whatsoever. We are not prepared to explain the absence of a greater tissue reaction in the skin of these mice. That it occurs in mice in the later migration of the young worm we have already shown (Section III of this monograph).

We believe that, if careful observations could be made on human beings at the time of infection and for the following forty-eight hours, the lesions of skin penetration of the cercaria of *Schistosoma japonicum* would be visible on thin skin surfaces, as they were in the case of our dog.

B. The lesions produced during migration of the parasite.

The pathological lesions produced by the young worm after it once gains access to a blood or lymph vessel are mainly those which occur after the worm meets obstruction in the capillaries. In the lymph stream it first reaches lymph nodes, where hemorrhages occur. We have found these both in mice and rabbits, but have not examined the lesions microscopically.

In the blood stream the first obstruction is met in the lungs, where extensive lesions are produced. Grossly they appear as hemorrhages, visible in rabbits and mice as early as twenty-four hours after infection, increasing up to the third day, and persisting in about the same degree until the fifth day, after which they slowly disappear (Section III of this monograph, Fig. 1). Their total duration depends largely upon the intensity of the infection. In a rabbit from which we recovered 3,213 worms on the tenth day after infection, the hemorrhages in the lungs were much less intense than those in a similar rabbit, five days after infection. On the other hand, a dog who succumbed to the disease fourteen days after infection still showed such extensive lesions of the lungs that they had the gross appearance of a diffuse hemorrhagic pneumonia. This dog yielded nearly 40,000 worms. Another dog, from whom over 10,000 worms were recovered on the thirty-third day after infection, had lungs of perfectly normal appearance. The duration of the lung lesions ultimately depends upon the speed with which the young worms escape from the lungs, or the length of time they are able to survive, if they become free in the lung tissue or alveoli. The lesion produced by any one worm would probably not

persist for more than four or five days in the loose tissue of the lung. Since the young worms probably all reach the lungs by the sixth day, these organs should be normal again, except in cases of hyperinfection, by the twelfth day after infection. Since the disease is never fatal to human beings in its early stages, no pathological observations are available for the period of lung involvement in man.

In light infections the lung lesions are discreet and therefore are more easily described. They appear as hemorrhages, scattered diffusely over the pleural surface of both lungs. In rabbits on the second day after infection they are not over 0.5 mm. in diameter. On the third day some have increased to 1 mm. or 1.5 mm. in diameter. They are sometimes sharp in outline, but sometimes fade gradually into normal lung tissue. They are not raised above the surface of the lung tissue, although, when they are confluent, the lungs are firm and contain much less than the normal amount of air. Cut surfaces of such a lung exude profuse bloody fluid. Individual lesions begin to fade about the fifth or sixth day, leaving, by the tenth day, a brownish stain on the pleura.

Our microscopic examinations of the earliest lung lesions are limited to those found in mice from the fourth to the seventh day after infection. The most prominent feature is hemorrhage, which occurs in localized areas distributed evenly on the fourth day, throughout the parenchyma. A few red blood cells are present in many alveoli which are not primarily involved. There is some phagocytosis of red blood cells in the alveoli by large wandering cells. There is intense congestion of the blood capillaries in the alveolar walls, and of the larger blood vessels. Many young forms of *Schistosoma japonicum* are found in arterioles and capillaries, and a smaller number are free in the alveolar cavities in the patches of hemorrhage (Fig. 3). Another prominent feature is edema of the spaces surrounding the larger blood vessels, especially the arteries, and, in some of these spaces, are seen dense accumulations of white blood cells, mostly polymorphonuclears, many of which are eosinophiles (Fig. 4). In the alveolar cavities, however, white blood cell accumulations are few in number and quite small. There seems to be no significant migration of white blood cells through the alveolar capillary walls. On the fifth day, the hemorrhages are more noticeable near the pleural surface of the lung than in the center. There are fewer worms in blood vessels and more in the lung parenchyma, and the perivascular edema and cell accumulation is less marked. On the sixth and seventh days there is progressively less hemorrhage, the young worms are much fewer, and the

perivascular reaction has entirely disappeared. At no time is there any irritation of the pleura, or any significant secretion into the bronchi.

In the hyperinfected dog which died fourteen days after infection, the microscopic sections of the lungs showed only very extensive fresh hemorrhage, with no remnants of broken-down red blood cells, as one would expect, if the bleeding had continued since the third day after infection. Here the larger blood vessels were intensely congested, especially the veins, but the capillaries of the alveolar walls seemed not to be distended. There was no white blood cell exudation. No young worms were found, although it is probable that, in such an intense infection, some had returned to the lungs from the liver, and might have been found in serial sections. The bronchi at the hilus of these lungs were filled with bloody mucus, but there was no inflammation of the bronchial or tracheal mucosa. It may be that the hemorrhagic appearance of these lungs was not a continuation of the lesions produced by the initial passage of the young worms through them, but was part of a general acute toxemia produced by the huge amount of foreign protein present in the blood. The necrosis of the liver and kidneys of this dog, which will be described below, add weight to this hypothesis.

The lesions in other organs than the lungs, due to the efforts of the young worms to reach the portal blood system, consist of hemorrhage, and of white blood cell accumulation about the individual parasites. Of these lesions hemorrhage is by far the most constant. It occurs whenever a young worm ruptures a capillary, perhaps sometimes without the actual escape of the worm from the vessel. We have observed these hemorrhages in rabbits beginning on the third day after infection and continuing through the tenth day. They are most profuse and easiest to demonstrate in the mucosa of the stomach, since the loose tissue there allows more diffusion of the blood and therefore larger hemorrhages. Here they vary from pin-point size to 3 mm. in diameter. Nevertheless, they are easily visible in all parts of the subcutaneous tissue, in the somatic muscles, the intestine, the kidneys, the diaphragm and the heart. They are most profuse on the fifth day after infection, and by the eighth day have disappeared from all the tissues except the mucosa of the stomach. We have demonstrated young worms in these hemorrhages in the rabbit's stomach and kidneys (Section III of this monograph, Figs. 2–7).

Cellular accumulations about young worms sometimes occur when the worms escape from blood vessels and lie free in the tissues. We

have already demonstrated such accumulation of mononuclear and polymorphonuclear leucocytes about a young worm in the diaphragm of a mouse, seven days after infection. The reaction is slight and is limited to the close proximity of the worm. Other worms do not have such a reaction about them. (Ibid., Figs. 8 and 9.) At this stage in the worm's migration and development, this reaction probably depends, as we have previously stated, upon the persistence of the proteolytic glands of the worm. These glands can no longer be demonstrated in worms which have reached the "delta" (δ) stage of development, which often occurs before they enter the portal blood vessels. Worms of this stage or later, therefore, would probably not be able to cause any local tissue reaction.

C. Lesions produced during maturation of the parasite.

The pathology of the period of maturation of the parasite in the veins of the portal system is negligible, except in cases of massive infection. Rabbits, killed on the eighth, ninth, tenth and eleventh days after infection, showed no diffuse liver lesions and only inconstant small collections of large mononuclear leucocytes in portal spaces or parenchyma, which may not have been due to this infection. Young worms, in portal radicles in the liver, were not surrounded by any tissue reaction. On the other hand, in a hyperinfected dog which succumbed to infection on the fourteenth day, definite lesions were found in the liver and kidney, which, we believe, were due to the toxins secreted by the parasite. In the liver, every portal radicle was choked with worms, even after nearly 40,000 worms had been recovered from the larger vessels of the portal system. Microscopically each liver lobule showed a large area of coagulative necrosis about the central vein, sometimes associated with hemorrhage (Fig. 5). The tissue of the portal spaces was swollen, possibly by edema. There was slight fat infiltration of the liver cells about the portal spaces. The remainder of the liver parenchyma was microscopically normal. There was no cellular infiltration. The kidneys of this dog were also extensively damaged. The proximal convoluted tubules, especially those near the capsule, presented an extreme degree of coagulative necrosis (Fig. 6). In some areas the glomeruli shared in this necrosis, and where this occurred the tissue was diffusely infiltrated with pseudo-eosinophilic polymorphonuclear leucocytes. No worms were found in the tissues. The spleen was congested, with small areas of hemorrhage into the pulp. Some of the splenic corpuscles were partly hyalinized. The only portion of the gastro-intestinal tract to show lesions was the duodenum, where

the mucosa contained hemorrhages and dense infiltration with polymorphonuclear leucocytes, many of which were eosinophiles. The other coats of the intestinal wall were normal, and no worms were found in the smaller veins.

II. The stage of egg deposition and extrusion.

Our observations on the pathology of this period of the disease were made on fourteen young dogs which died or were killed at various times, from twenty-eight to one hundred and nineteen days after infection. This is the period during which the real pathology of the disease is developed, and in which, clinically, the acute symptoms are manifested. The nature of the lesions is dependent upon two main factors: first, the biological activity of the male and female parasites in their migration and in their reproductive activity; and second, the action on the tissues of the eggs, after their escape from the female worm. The first of these factors, the biological activity of the parasites, is the only factor which makes the pathology of the Japanese form of schistosomiasis different from that of schistosomiasis hematobia and schistosomiasis mansoni, for the reaction of the tissues to the eggs deposited in them is identical in the three forms of infection.

In the biological activity of the parasites there are two features which influence the resulting pathology. The first of these is the strange phenomenon that the worm seeks certain organs for the deposition of its eggs. Why *S. hematobium* should seek primarily the wall of the urinary bladder, while *S. mansoni* and *S. japonicum* confine themselves entirely to the walls of the alimentary tract, especially the colon and rectum, is a problem of great biological interest which cannot concern us here. Its importance to the pathologist is that it makes the former a clinical disease mainly of the urinary organs, while it causes the two latter infections to produce clinical disease of the intestines and liver.

The second feature which influences the pathology, produced by the parasites, is the difference in the egg-producing ability of the females of the three species. This is the feature which makes schistosomiasis japonica so much more serious a disease than schistosomiasis mansoni. For whereas, according to Fairley, no more than two ova have been counted by him in the uterus of a female *S. mansoni*, we have counted in ten female specimens of *S. japonicum*, which were only thirty-three days beyond the cercaria stage, an average of 161 ova, with a maximum of 233. Although this may not be an absolute com-

parison between the egg-producing powers of the two worms, it gives some idea of the differences to be expected in the bodies of infected mammalian hosts.

A. The mechanism of egg deposition.

The exact mechanism of egg deposition by the schistosomes is very difficult to determine. Hypotheses have been advanced by various investigators, notably Letulle (1905), Looss (1908) and Fairley (1920). All these hypotheses are based, either upon observations of the worms in visible veins on the peritoneal surface of the viscus involved, or upon the position of eggs in the tissues, after they have been deposited. The observation of worms in veins on the peritoneal coat of the intestine is not satisfactory, since most of the ova are deposited by the worms deep in the wall, where they cannot be seen from the peritoneal surface. Observation of the eggs, after deposition, is also inaccurate, because the withdrawal of the worm from the smallest veins after depositing the ova allows the collapse of distended capillaries and venules, and alters the relation of various structures in the wall of the intestine. Furthermore, the mechanism may be different in the different species, for the delivery of one or two ova at a time, as is probably the case with *S. mansoni*, is quite a different process than delivering one or two hundred eggs within a short space of time, as is apparently done by *S. japonicum*. We had expected that serial sections of blocks of intestine, removed from heavily infected living animals soon after eggs began to appear in the feces, would show worms in the actual process of egg deposition. So far, however, in several thousand sections examined, we have failed to find a place which even suggested that the worm in the section had just deposited the ova seen in the section. We believe that only the most rapid and complete fixation of the tissues would give a true picture of the actual condition at the time of removing the section of intestine, and we have not yet been able to develop the technique necessary for reliable observations. Our specimens do present evidence, however, which permits us to draw certain definite conclusions.

The young worms begin to migrate from the portal vein out into the larger mesenteric veins, relatively early in their development. In hyperinfections this probably occurs earlier than in light infections, just as eggs appear earlier in the feces in hyperinfected animals. In two of our dogs, which died of distemper twenty-three days after infection, worms were recovered from the mesenteric veins and portal veins in the following numbers:

Dog A, mesenteric veins 109, portal veins 24.
Dog B, " " 340, " " 11.

In another dog, heavily infected, which died twenty-five days after infection, a few male worms were found in serial sections of the ileum, in the submucosa. They were not found in copulation with females, however, either in this locality or in the larger mesenteric or the portal veins, on gross dissection.

Our next dog, in point of duration of infection, was killed, while in apparently excellent health, twenty-eight days after infection. This dog had passed eggs in the feces the day before, and was sacrificed for the purpose of ascertaining the exact mechanism of egg deposition. Although this has not been absolutely accomplished, we gained information which comes close to solving the problem. Male and female worms were found in large numbers in the smaller branches of the mesenteric veins, often disappearing within the muscular coat of the intestinal wall. Sections of intestine were excised, while the animal was still alive, under ether anesthesia, and, without being opened, were fixed at once in Zenker's solution. Serial sections of these blocks showed innumerable collections of eggs in the mucosa and submucosa, a few of which were already surrounded by a tissue reaction consisting of polymorphonuclear and mononuclear leucocytes. In the veins at the mesenteric attachment of the intestine, and sometimes in the veins of the submucosa, were male and female worms. Those in the submucosa were always in copulation, with the heads of the two worms at approximately the same depth of penetration into the vein. In no case did we find, as Fairley has described in monkeys infected with *S. hematobium* and *S. mansoni*, the female advanced in the vessel beyond the position of the male. Neither did we find any hemorrhage in any part of the intestine wall, as though eggs had been cast out from a vessel into the surrounding tissues. The thin-walled venules of the submucosa have an astonishing capacity for dilatation in order to accommodate the male and female worms *in copula*. Undoubtedly the worms had retracted somewhat from their position of egg deposition, possibly after the tissue was immersed in the fixative. In the egg-laying position the head of the female may have been extended considerably beyond that of the male into the smaller venules of the submucosa, or even into those of the mucosa, but we feel sure that the female must still have been held within the gynecophoral canal of the male during the act of egg deposition.

This differs from Fairley's conception of the deposition of ova by the female of *S. hematobium* and *S. mansoni*. He concludes, from his

observations in experimentally infected monkeys, that the female leaves the male, advances into a vessel too small to accommodate the male, deposits one egg at a time and withdraws in the vessel after each egg deposition so that the vessel has the appearance of a chain of beads, the eggs being in a single row in the vessel. Our findings, now to be described, seem to show that the process is somewhat different in the case of *S. japonicum*.

The deposited eggs in the intestinal wall of our twenty-eight-day dog were all in the mucosa and submucosa. By far the larger number were in the mucosa. Study of the various groups of eggs showed that there were from about ten to about two hundred in each group, and that the groups usually radiated out in rows in the stroma of the mucosa from a central point in the submucosa. The eggs were usually crowded close together, sometimes in a single row, sometimes in more irregular masses. They usually extended about half way into the mucosa toward the lumen of the intestine, but sometimes the farthest ones were quite close to the lumen. They were invariably in the stroma, rather than in the lumen of intestinal glands, and in some places were definitely located within dilated capillaries (Figs. 7 and 8). This arrangement was so characteristic that we feel sure that practically all the eggs at this stage were in capillaries, although the capillary wall was often difficult to distinguish. In the superficial portions of the mucosa some of the capillaries were intensely congested, while in other adjacent areas they were collapsed.

In each group of deposited eggs various stages of development of the miracidium within the egg could be made out (Fig. 9). Some seemed fully developed, while others were collapsed and contained little or no organized material. In no case did we find hemorrhage into the tissues, as would have occurred had the eggs burst out from the blood vessels during the act of deposition. About most of the eggs there was no reaction of the host's tissues, but about some of the fully developed eggs were small accumulations of cells, mostly polymorphonuclear leucocytes, with a smaller number of large and small mononuclear cells. There were also a few larger areas of diffuse polynuclear infiltration of the stroma of the mucosa, compressing the intestinal glands (Fig. 10). These areas were not so definitely associated with well-developed eggs, which suggested that they were caused by some other poison than that secreted by the egg. This we shall discuss later.

The significance of the above-described arrangement of the recently deposited eggs may be summed up as follows: First, that they are

deposited by a worm whose head is in a distended vein of the submucosa or mucosa. Second, that the worm deposits a large number of ova at one time, expelling them distally into the capillaries of the mucosa. Third, that the eggs are thus originally deposited very close to the lumen of the intestine, where, by the slightest reaction on their own part, or perhaps merely by the casting off of a bit of intestinal epithelium, they gain the intestinal lumen. In these conclusions we are in agreement with Looss (1908, p. 169), in his observations in human cases of Egyptian schistosomiasis. We may add that we consider it possible that a few eggs thus deposited may cause immediate rupture of the surface epithelium of the intestine, thus gaining the lumen practically at the moment of deposition.

Two more facts must be emphasized at this point which confirm our theory of the method of egg deposition. In the first place, the finding of very young eggs in the various groups suggests that these eggs had not long been formed, that they probably came quickly from the deep portion of the uterus of the worm, and that, therefore, the worm often expelled most of the worms from its uterus at one time. The large number of eggs found in many of the groups confirms this.

The second fact to be emphasized is that the eggs which this dog discharged in its feces on the day before death, must have been deposited by the female worms a very short time before. Previous to the observation of this dog, our opinion had been that no eggs were deposited by *S. japonicum* before the twenty-eighth day of its intramammalian existence (Section II of this monograph). This opinion was based upon the observation of many infected dogs and mice. The fact that this dog passed eggs in its feces on the twenty-seventh day after infection indicates, therefore, that the time required for the passage of eggs from the worm to the lumen of the intestine must sometimes be very short.

The rôle played by the spine of the egg of *S. hematobium* and *S. mansoni* has received considerable attention by writers on the mechanism by which the eggs of those parasites reach the lumen of the intestine. It has been held by some that the spine is an important factor, both in enabling the egg to break out from the capillary in which it is deposited, and in working its way through the tissues. Others, including Fairley (1920), ascribe to the spine importance only in the escape of the egg from the blood vessel. While it is probable that the spine must have some influence on the position of the egg in the blood vessel, we wish to emphasize the point that the egg of *S. japonicum* has only a rudimentary spine, and yet its ability to

escape from the blood vessel and to escape rapidly into the lumen of the intestine seems to be fully equal to that of the eggs of the other two species. It seems probable that an egg with a prominent spine, when once deposited in a small vein, would be less likely to escape into the blood stream and thence into the liver, than an egg with a rudimentary spine. We believe, however, that, from a practical standpoint, this difference is negligible, and that most of the eggs which reach the liver are deposited by the worms directly into larger blood vessels (Fig. 11).

B. The development of the intestinal lesions.

By the thirty-third day after infection the intestine of a hyperinfected dog is diffusely congested on the mucosal surface and may show minute points of hemorrhage. Microscopically most of the ova are still confined to the submucosa and mucosa (Fig. 12), but a few are found lying in capillaries or open spaces within the muscular layers. More of the eggs contain well-formed miracidia than in the twenty-eight-day dog, and with this development within the egg, the relation of some of the eggs to capillaries is lost, and they become surrounded by collections of polynuclear leucocytes. These beginning abscesses are somewhat larger in the submucosa than in the mucosa.

By the fortieth day a new feature has appeared in the gross appearance of the intestines. This is the development of lesions on the serous surface. These lesions are small spindle-shaped yellow areas, with their long axes transverse, lying apparently between bundles of the transverse muscle of the intestine. They are usually not close to the mesentery and may even be on the opposite side of the intestine. Although they may be slightly raised above the surrounding tissue, there is, at this stage, no inflammation of the peritoneal surface. Microscopically these lesions are the extension of the egg deposits, with their surrounding leucocyte accumulations, into the muscular coats of the intestine (Fig. 13). They may be direct extensions of abscesses which have begun in the submucosa, or may have, as their nucleus, eggs deposited directly in the muscularis. The muscle tissue seems to have melted away in the process of abscess formation, although there is also some evidence of compression of tissue by the invading cells. There may be hyalinization of small areas of smooth muscle cells. There is also in some places infiltration of normal smooth muscle tissue by polymorphonuclear leucocytes. The proportion of eosinophiles among the invading leucocytes is large, and is more noticeable than in the earlier stages. At the centers of these

abscesses there may be some fragmentation of leucocytes, but there is never such a definite area of necrosis as one would find in either a pyogenic abscess or a tuberculous abscess of the same size.

Meanwhile the lesions in the mucosa and submucosa have also advanced. In the submucosa the largest lesions are found, similar in type to those just described. They are large enough to have pushed out the mucosa in places, so that on gross section the intestinal wall is definitely thickened. Some have burst through the muscularis mucosae into the mucosa, perhaps because of their continuity with ova lying in the mucosa, about which the same process is developing. Other abscesses have formed primarily in the mucosa, and some have burst out through the intestinal glands into the lumen. Some of the deeper glands seem to be expanded into cystic cavities, packed with pus cells. In the pus escaping into the intestine occasional eggs are present. At this stage we find no evidence of beginning repair, by the formation of connective tissue, which is so prominent later on. We did find in this dog, however, the first evidences of proliferation of intestinal gland epithelium into the submucosa, which we believe is the basis for the development of intestinal papillomata, and which we will describe later in more detail.

Dogs which survive beyond this period are necessarily less heavily infected than those we have thus far described. The size of the individual lesions increases, however, so that they often produce considerable thickening of the intestinal wall. On the peritoneal surface the yellow, spindle-shaped areas become larger, and when the inflammation reaches the peritoneum itself, hyperemia or slight hemorrhage occurs, fibrin forms on the surface, and occasionally mesentery or omentum is found attached to the lesion with the formation of a fibrous adhesion. On the mucosal surface there are local areas of hyperemia about the lesions, occasional minute hemorrhages, and small masses of bloody mucus and pus. No ulceration of macroscopic size has been observed by us in any of our experimental dogs.

Microscopically (Fig. 14) the further increase in the size of the lesions is accompanied by their extension, usually through a connective tissue septum, from the muscularis outward to the peritoneal surface, where they develop nodules, composed of polymorphonuclear leucocytes, in the center of which one or more eggs is located (Fig. 15). On this free surface the reaction of repair is very rapid, with the production of fibroblasts tending to encapsulate the abscess (Fig. 16).

The repair process also appears soon in the muscularis and submucosa. In the latter layer it is perhaps encouraged by the evacua-

tion of some of the pus from the abscesses into the mucosa and lumen of the intestine. Fibroblasts become numerous at the periphery of the abscesses, and in some places invade the mass of leucocytes.

C. Epithelial proliferation into the submucosa.

The next dog whose intestine was studied in serial section died sixty-five days after infection. Besides the full development of the lesions just described, this dog presented the phenomenon of proliferation of the glandular epithelium of the intestine into the abscess cavities of the submucosa. Although a similar proliferation has been described by Ferguson (1911) in the bladder, in human cases of infection by *S. hematobium,* it has not been described, so far as we know, in *S. japonicum* or *S. mansoni* infection. Its significance lies in its probable relation to the development of intestinal papillomata, which are so common in late stages of these diseases, and which are sometimes suspected of being associated with adenocarcinoma of the intestine. Fairley (1920) did not find epithelial proliferation into the submucosa in any of his experimentally infected monkeys, although he did observe protrusions of the mucosa above lesions in the submucosa, which he interpreted as the beginnings of papillomata.

In serial sections of this dog's intestine the glands adjacent to abscesses in the submucosa had proliferated downward into what appeared to be the scar resulting from an earlier abscess (Fig. 17). In other places abscess cavities were connected directly with the lumen of glands at their base, and here the glandular epithelium had proliferated along the periphery of the abscess, sometimes entirely surrounding the cavity, which was still filled with leucocytes (Figs. 18 and 19), sometimes tapering off from columnar to cuboidal and finally to flattened, undifferentiated epithelium, very similar to the manner in which skin epithelium grows out over a granulating wound (Figs. 20 and 21). In the latter case the remainder of the abscess was bounded by the fibrous tissue of the submucosa or, deeper, by the muscularis. By lining the cavity of such an abscess with the epithelium of the intestine the evacuation of the contents of the abscess through a small opening was apparently facilitated. Most of these epithelial proliferations occurred where the submucosa was normally thick, and where there was, therefore, a natural projection of the mucosa into the intestinal lumen. Some abscess cavities had more than one outlet, on various aspects of the epithelial projection, and it therefore seems reasonable to assume that such a process may be the basis for the formation of a papilloma. There is doubtless also the

additional factor, in the papilloma formation, of outward proliferation of epithelium, due to the presence of eggs in the stroma of the mucosa.

D. The schistosomiasis abscess.

There are several characteristics of the abscesses which occur in the wall of the intestine which deserve special mention because of their difference from any other kind of pyogenic lesion.

1. The abscesses always contain eggs of *Schistosoma japonicum.* This leads to the conclusion that they are caused by the presence of the eggs. It is evident, too, that the abscesses appear to develop during the secretive activity of the miracidium within the egg. We have described in a previous paper the two types of glands possessed by the miracidium (Section II of this monograph). The mucoid glands whose ducts discharge their secretion on the antero-lateral aspect of the miracidium apparently become active long before the miracidium is ready to leave the egg. Mucoid material is seen within the shell, and the adhesion of particles of intestinal contents to discharged eggs shows that the egg has become sticky externally, probably from the escape of this mucoid secretion through the porous shell. We believe that it is this material which acts as a pyogenic toxin in the host's tissues. It is secreted as long as the miracidium is alive. After it is no longer secreted the abscess undergoes organization and fibrosis, and the scar tissue holds within it the dead egg.

2. The relatively large size of abscesses, particularly in the submucosa and muscularis, which apparently contain very few eggs, leads to the query whether or not the abscess may be partly caused by direct secretions from the male or female worm. The possible source of such secretion in the male would be the alimentary tract, the secretion being probably the same as that which acts on the red blood cells. From the female, in addition to this secretion, there is the possibility of a secretion from the genital tract, discharged at the time of egg deposition. There is no visible evidence that any secretion from the alimentary tract of the worm is deposited in the tissues. There is some evidence, however, that the female worm may occasionally discharge toxic material from its uterus during egg deposition. This is suggested by the occurrence of a few abscesses in the mucosa, associated with hemorrhage, but not containing eggs, and found in the earliest period of egg deposition. This we have already mentioned (Fig. 10).

3. The cellular contents of the abscesses consist mainly of polymorphonuclear leucocytes, a considerable proportion of which are

eosinophiles. Large mononuclear leucocytes and lymphocytes are also present in small numbers.

4. The abscesses never undergo necrosis. Apparently the toxin, although it dissolves fixed tissues, has no such power against the wandering cells which are attracted by it. Another factor which probably acts to prevent the progress of the abscess to necrosis is the fact that the toxins act only from the point of their original production. Since there is no multiplication of the organism producing the toxin, as there is in abscesses of bacterial origin, the toxin is greatly diluted at the periphery of the abscess, a condition which may stimulate the formation of fibroblasts.

5. If these abscesses break through into the lumen of the intestine they discharge their contents through small openings between the intestinal glands. There is no massive destruction of the mucosa with ulcer formation. The limitation of the action of the toxin, secreted by the egg, is also probably responsible for this conservative method of discharge.

6. There is a tendency to rapid repair of the injured tissue, with the formation of abundant granulation tissue and dense scars. Even as early as sixty-five days after infection, the submucosa is considerably thickened by abundant scar tissue. Where abscesses discharge their contents into the lumen of the intestine the cavity collapses, so that the scar is relatively small. Where the contents of the abscess are not discharged, however, the early fibroblastic reaction at the periphery proceeds toward the center of the abscess more slowly, and we have the structure commonly known as the "schistosomiasis tubercle." The persistence of the eggs and leucocytes affords a structure into which the fibroblasts grow in abundance, so that the productive reaction ultimately forms a definite nodule of fibrous tissue. The eggs die and later their shells collapse, foreign-body giant cells form about them, and the leucocytes gradually migrate away and are seen in the surrounding tissue. The late stage, with foreign body giant cells, has not been found, however, in our experimental dogs. It will be further discussed in relation to late human cases of the disease.

E. The distribution of intestinal lesions in experimental dogs.

In all of our experimental dogs the jejunum was the portion of the alimentary tract most intensely involved. Lesions were progressively fewer in number through the ileum toward the colon and were uncommon in the duodenum. The colon was lightly involved with local lesions, but its mucosa was usually intensely congested and was often

covered with mucus. The reason for this intense congestion was not apparent in microscopic sections, but may have been due to the congestion of the larger inferior mesenteric veins which often contained many worms. The stomach occasionally showed isolated lesions due to egg deposits, and in hyperinfected dogs the gastric veins were crowded with worms. This distribution of intestinal lesions is in contrast to that found in human infections, where the colon is the part most involved.

F. The pathology in other organs in experimental dogs.

Liver. As soon as eggs are deposited by the worm, some of them become free in the portal blood stream and are carried to the liver. Although most of the eggs are undoubtedly discharged into the capillaries and smaller venules of the intestinal wall, it is reasonable to suppose that some may escape from adult worms, even while the worms are in the larger mesenteric veins. In a uterus containing two hundred or more eggs, the more advanced eggs are crowded forward toward the genital opening and might be expected to escape in small number, without regard to the position of the worm (Fig. 22).

The gross changes in the livers of our experimental dogs during the period of egg deposition consisted of the occurrence of minute localized lesions, red in early cases, gray or white in later cases, and measuring up to one millimeter in diameter.

Microscopically these lesions are the abscesses and tubercles produced by the presence of the eggs in the liver tissue. The development of the lesions is fundamentally the same as in the intestine, but there are differences caused by the difference in the tissue invaded. In our twenty-eight-day dog, the eggs were present in the interlobular portal veins, merely as emboli, surrounded by no reaction whatsoever. Newly deposited eggs in later dogs also showed no tissue reaction (Fig. 23). In the thirty-three-day dog many of the eggs were surrounded by collections of leucocytes, so dense that the other structures of the portal space were no longer distinguishable. The cellular accumulations about the eggs were similar to those in the intestines, polymorphonuclear leucocytes being the predominant cells, and a considerable proportion being eosinophiles. In the forty-day dog, however, the most advanced lesions were of two varieties. In one type the size of the abscess had increased considerably, the cells at the center had become degenerated, with pyknosis and fragmentation of their nuclei, while at the periphery there was very little organization of fibrous tissue, and the liver tissue was somewhat compressed by the

leucocytic accumulation (Fig. 24). The other type of lesion was much smaller, the leucocytes were largely replaced by fibroblasts and large mononuclear leucocytes, and there was a definite tendency to encapsulate the contained egg (Fig. 25). In some of these lesions the bile ducts of the portal spaces were still visible. In later dogs there was very little progress in the lesions beyond the point described. The only important change was the development of occasional foreign-body giant cells within the "tubercles." The first indication of these was a grouping of large cells with pale-staining oval nuclei about an egg. Other "tubercles" showed definite giant cells with peripherally arranged nuclei of this same type (Fig. 26).

In only one of our dogs did we find any tendency to cirrhosis of the liver, independent of the lesions produced by eggs. The dog which died forty days after infection showed marked edema of the fibrous tissue of the portal spaces and an apparent increase of the fibrous tissue itself (Fig. 27). This was limited to the portal spaces and did not appear to be of recent origin. Since we did not find it in later dogs, even up to 119 days after infection, we hesitate to ascribe it to the schistosome infection. This absence of a diffuse fibrosis in most of our dogs differs from the findings of Fairley (1920) in monkeys, experimentally infected with *S. hematobium* and *S. mansoni*. He constantly found a diffuse fibrosis associated with the portal spaces, independent of the presence of ova in the tissues. He does not state how soon after infection it was first demonstrable, but he shows a drawing of such a lesion found sixty-two days after infection.

The only other cellular reaction in the liver was in the form of small accumulations of polymorphonuclear leucocytes in the blood capillaries of the parenchyma, in our twenty-eight-day dog. These did not appear in later infections.

A second constant microscopic finding in the livers of our dogs was the presence of hematin pigment, undoubtedly discharged from the alimentary canal of the adult worms after their digestion of the host's red blood cells. This pigment is golden brown in color, and occurs in irregular masses of varying size. It was found in the endothelial cells of the blood capillaries of the liver parenchyma, in large phagocytic cells in the portal spaces, and in similar cells in the organizing portions of the "tubercles" (Figs. 28 and 29). Fairley (1920) called attention to this pigment in monkey and human cases of *S. hematobium* and *S. mansoni* infection, and determined the nature of the pigment by solubility experiments, as previously outlined by Brown (1911) for malarial pigment. We have corroborated Fairley's findings in

solubility experiments with the pigment in *S. japonicum* infections. Since the pigment is slight in amount, as compared with that in the spleen in fatal cases of malaria, the spectroscopic test advocated by Brown is difficult to perform, although a very light brown solution is obtained by extracting pieces of liver in 0.04 per cent. alcoholic potash. However, its solubilities and the absence of response to the ordinary ferrocyanide test for hemosiderin are easy to demonstrate in Zenker-fixed microscopic sections, which designates it probably as *hematin.* We have also performed these solubility tests, as outlined by Brown, on adult worms and have obtained similar results.

It is appropriate at this point to comment briefly on the visible digestive activity of the adult worms. We have observed in sections of male and female worms in the veins of the host, that most of the ingested red blood cells become disintegrated and changed to hematin immediately posterior to the esophagus of the worm. This condition persists as far back as the end of the cecum, the whole tract being filled with black pigment. In striking contrast to this is the remarkably well-preserved condition of the polymorphonuclear leucocytes within the worm's gut (Fig. 30). Their nuclei are well preserved, and their cytoplasm can be definitely distinguished. This condition sometimes applies to these cells even in the posterior end of the cecum, although here they are fewer in number. Mononuclear leucocytes have not been observed within the worms. Apparently the digestive secretion of the worm acts powerfully upon the red blood cells, but has much less effect upon the granular leucocytes. It is conceivable that these cells may be extruded again by the worm.

Spleen. The changes in this organ were less constant and less easily interpreted than those in the organs so far described. In hyper-infected dogs, dying on or before the thirty-third day, the only change noted was congestion. The degree of congestion was dependent upon the intensity of the infection. The spleen of the twenty-eight-day dog was greatly enlarged. It collapsed to about half its former size upon removal, and even then weighed twenty-seven grams, which was about five times the normal weight for that dog. Microscopically there were small hemorrhages in the pulp and splenic corpuscles, as well as intense congestion of all the blood vessels.

Hematin first appeared in the spleen in our forty-day dog. It was less in amount than in the liver, and was usually in small granules. It was found in endothelial cells of the spleen pulp and in a few large mononuclear phagocytes. From this time on it was present in somewhat larger amount, but was never as abundant as in the liver.

Increase of the fibrous reticulum of the spleen was not observed until sixty-three days after infection (Fig. 31). It was most marked in two spleens which were much reduced in size, each weighing about two grams, where five grams would have been the normal size. It may be, therefore, that the increase of fibrous tissue was partly relative. However, the splenic corpuscles were decreased in size and were invaded by fibroblasts, and the pulp contained very few lymphocytes, leucocytes or red blood cells. The predominating cell had a large pale-staining oval nucleus and scant cytoplasm, and was apparently a fibroblast. There was some thickening of the walls of small blood vessels in the pulp. The blood sinuses of the pulp were difficult to distinguish, however, and were not dilated. In these two points, as well as in size, these spleens differed from the enlarged spleens found in late human cases.

Mesenteric lymph nodes. Enlargement of the lymph nodes draining the entire intestine was a constant finding in our experimental dogs. They were often as large as two centimeters in diameter. Usually they were pink in color, but were sometimes deep red. They were soft in consistency. Microscopically, edema was the most prominent feature. With this there was usually loss of most of the active lymphoid tissue. The sinuses were widely dilated, containing coagulum and a great variety of cells. Lymphocytes, macrophages and polymorphonuclear leucocytes were the most numerous cells. Eosinophiles were not conspicuous. No schistosome eggs were found in the sections.

Lungs. The uniformly normal gross and microscopic appearance of the lungs was an important finding in our dogs. The only abnormal condition encountered was the presence of a male worm in an artery of the lung of a dog dying twenty-five days after infection. Such a worm might have reached the lung either by leaving the portal system of veins through a pelvic anastomosis with the systemic veins and thence being carried through the vena cava to the heart and pulmonary artery, or it might have worked its way through the parenchyma of the liver to an hepatic vein and thence reached the vena cava. The former path seems to us the most reasonable. Either course is a decidedly anomalous act on the part of *Schistosoma japonicum*, although the former course is said to be the route by which *Schistosoma hematobium* reaches its natural habitat in the vesical veins.

Eggs of *S. japonicum* were not found in any of the lung sections examined, but it is reasonable to suppose that an occasional egg might reach an hepatic vein by the rupture of an abscess in the liver into the vein of a lobule. Fairley (1920) macerated the organs of some of his

monkeys experimentally infected with *S. mansoni*, using sodium hydroxide solution to dissolve the soft tissues. He found most of the ova deposited in the colon, liver and small intestine, but also found a few in the lungs, as well as in the stomach, gall bladder, pancreas, spleen, urinary bladder, lymph glands, kidneys, suprarenal glands and myocardium.

Kidneys. No uniform changes which could be ascribed to infection by *S. japonicum* have been found.

Bladder. Normal. No specimens of *S. japonicum* were found in the vesical veins, although they were sometimes present in the inferior mesenteric veins close by.

Pancreas. Consistently normal, although worms were occasionally found in the veins of this organ in hyperinfected dogs which died early in the course of the infection.

III. The stage of tissue proliferation and repair.

Except for the beginning of fibroblastic proliferation which we have already described in the lesions in our dogs, our observations of the stage of tissue proliferation and repair are confined to material from three human cases of schistosomiasis japonica. Since the disease is probably never fatal to human beings solely as a result of the toxins produced during the period of egg deposition and extrusion, the factor of scar formation is an important and prominent one in the pathology of human cases. On the other hand, the picture seen at necropsy in human cases is not purely that of the stage of scar formation, for most of the persons who die of this disease have been repeatedly infected, and in them the stage of egg deposition is still present at death. We therefore see, as a rule, in human tissues all stages of reaction to the deposition of eggs, as well as the end result of egg deposition in the past. The principal end result in human cases is cirrhosis of the liver which so obstructs the portal circulation that a massive ascites is produced, and with this the poorly understood nutritional disturbances which lead to weakness, emaciation and, finally, death.

Intestines. The distribution of the intestinal lesions in late human cases is distinctly different from that in our dogs. The small intestine is only slightly involved, and these lesions are usually confined to the ileum. Grossly there is usually nothing more than a slight thickening of the ileum. In the colon the lesions increase in intensity from the cecum to the sigmoid colon and rectum. Externally there is often a matting together of the omentum into a thick fibrous mass, often adherent to some portion of the colon. The wall of the colon

is irregularly thickened, with enlargement and fusion of many of the appendices epiploicae. The thickening is greatest toward the mesenteric attachment, but may involve the whole circumference, especially in the sigmoid colon, producing a stiff solid tube. The mesentery is thickened and shortened, often difficult to displace from its position. This thickening extends upward toward the base of the mesentery of the small intestine, and may extend to the attachment of the small intestine. Beside the thickening of the wall of the colon itself, this organ may present round, solid, tumor-like masses on its peritoneal surface. On gross section these are seen to be fibrous nodules, often containing areas of apparent necrosis, and usually showing brown spots where groups of eggs are deposited.

The colon itself, on gross section, presents a much thickened wall, in which the muscle layers are seen to be invaded and bounded internally and externally by thickened layers of fibrous tissue. The submucosa varies greatly in thickness and its consistency and mobility are proportional to its thickness. Through the white firm fibrous tissue can be seen many small areas of yellow softer material, often traversed by bands of fibrous tissue, and innumerable brown spots which indicate the location of egg deposits. The mucosa in many places has lost its regular arrangement of rugae, and instead it presents an uneven surface on which are all grades of papillary projections of the epithelium from minute spots barely raised above the surface to broad firm slightly-raised masses and pedunculated papillomata, perhaps a centimeter in length (Fig. 32). There may be minute points of hemorrhage, where eggs or abscesses are breaking through to the surface. Shallow ulcers are described, but were not present in our cases.

Microscopically the appearance of the intestinal wall is only different from that described in our experimental dogs, in that there is a massive increase in fibrous tissue, involving all layers of the organ, but especially the submucosa. The fibrous tissue is diffuse, but, where conditions have been favorable, a spherical tubercle-like mass has developed, enclosing a few eggs and surrounding the organized abscess by a ring of fibrous tissue (Fig. 33). Eggs are present, as before, in all layers of the wall, often in large groups (Fig. 34). Some are still immature and seem never to have produced a reaction in the surrounding tissue. Others are in the midst of their activity and are surrounded by polymorphonuclear leucocytes. Still others have been caught in the scar tissue and have either become calcified or are surrounded by foreign-body giant cells (Fig. 35). Some have even been invaded by

giant cells, which often occupy the egg shell, as the miracidium formerly did, and may be mistaken for it (Fig. 36).

The papillomata consist, microscopically, of a core of submucosa, surmounted by relatively normal mucosa. The submucosa usually contains numerous eggs of *Schistosoma japonicum*, most of which have passed the stage of activity and are imbedded in scar tissue. In the mucosa, also, there may be large numbers of eggs, some still retaining the arrangement in single file in which they were deposited by the worm, others in areas of mucosal stroma, where the glands are now missing and where scar tissue or giant cells are already developed. The epithelium covering these papillomata usually shows little tendency to adenomatous proliferation, although sections cut obliquely through a papilloma may at first suggest this. We have not seen the proliferation of epithelium into the abscesses of the submucosa which we have already described in our experimental dogs. It may have been described, however, by the Japanese in literature which has not yet become available to us. It has not been seen in human cases of schistosomiasis mansoni, although the bladder lesions have shown it in schistosomiasis hematobia.

Carcinoma of the colon and rectum has been described by several Japanese writers in persons infected with *S. japonicum* (Endo, 1908; Fukushima, 1914). The stimulus to epithelial proliferation which we have described in dogs would seem to be a possible starting point for such a malignant change. Besides this, the fully developed papillomata, because of their exposure to injury in the intestinal lumen, might also undergo such a change. Certainly the presence of an irritating foreign body within the tissues, which produces leucocytic reaction, giant-cell formation and epithelial proliferation, is an ideal basis for the development of a malignant tumor.

The mesentery shows, microscopically, a fibrous thickening in which eggs may be found singly or in masses, and there may be small tubercles protruding outward on the peritoneal surface. The relation of the eggs to blood or lymph vessels is difficult to determine, but it is probable that some eggs are carried to such locations through lymph vessels into which abscesses in the intestinal wall have broken, while others have been deposited directly into blood vessels in the mesentery by worms which could no longer reach the scarred wall of the intestine. The progressive extension of the egg deposits from the intestinal mucosa outward to other localities in the body, as the duration of the infection increases, is one of the interesting phenomena of this disease.

The mesenteric veins, besides containing specimens of *S. japonicum*,

sometimes contain thrombi, usually in the larger branches. The main portal vein itself and its larger branches in the liver are even more liable to thrombosis, probably because of the frequent accumulation of many worms there. Such thrombi may extend out into the splenic vein and may be an important factor in the massive enlargement of the spleen in some cases of this disease.

Mesenteric and retroperitoneal lymph nodes. Since these nodes are the first filter in the lymph drainage of the intestine they receive much of the products of the infection. They are always found enlarged, and are either fibrous or edematous. They are often of a brownish tint on cut section, due to the eggs which have been carried to them in the lymph stream. Microscopically their lymphoid tissue is decreased in amount, and active follicles may be entirely missing. Eggs may or may not be surrounded by the characteristic reaction. The lymph sinuses are usually dilated and contain a variety of cells among which large macrophages, containing broken-down leucocytes, are prominent. Some lymph nodes are transformed into masses of scar tissue firmly embedded in the surrounding fat.

Liver. This organ often presents a most extraordinary picture, which adequately explains its part in the production of the late symptoms of the disease. In size, it may be considerably enlarged or slightly shrunken. In our three cases the liver weighed 1943, 1485 and 1420 grams respectively. It is characteristic to find a hard irregular projection of the left lobe extending below the costal arch in the midline. The organ is irregular in shape, presenting nodular swellings ranging up to 3 cm. in diameter, and deep fissures and scars often extending 1 cm. into its substance. The left lobe is often proportionately larger than the right, although it is difficult to see any difference in the degree of involvement of the two lobes. In consistency the organ is very hard, although the hyperplasia of new liver tissue may make it normal in some places. The capsule may be diffusely thickened into a white fibrous coat, or the thickening may be limited to small areas. In one of our cases the entire exterior of the organ was gray and fibrous with many pock-like depressions in the thickened capsule. There are usually fibrous tags on the surface, representing old adhesions to the parietal peritoneum or adjacent intestines. The ligaments are often thickened, particularly the falciform ligament, which may contain enlarged veins for collateral drainage. The gall bladder wall may be thickened, due to its close association with the capsule of the liver and perhaps to the deposit of eggs in its wall.

The cut surface of the liver varies in appearance with the intensity

and duration of the disease. In mild cases it may be marked by only a few small scars, usually near the surface of the organ. In more severe cases there is a definite diffuse increase of fibrous tissue, somewhat coarser in distribution than in the typical "hobnail" liver of nodular cirrhosis. Normal or fatty liver tissue between the fibrous strands suggests the persistence of considerable functional capacity in the organ. Extreme cases show massive destruction of liver tissue with replacement by scars (Fig. 37). The remaining liver tissue shows the finer scars of interlobular cirrhosis, and in some places shows localized areas of dilatation of blood capillaries and bile ducts. There is also a marked thickening of the walls of the portal vein and its branches extending from the hilus of the liver to the subcapsular regions. This has been described as the typical condition of the liver in *S. mansoni* infections, and was called by Symmers (1904) a "clay pipe-stem cirrhosis." (Fig. 37.) This thickening of the larger veins is not due to the deposit of eggs in their walls, but has been attributed by Fairley (1920) mainly to toxins secreted by the adult worm. Although such a substance is probably an important factor, we believe that additional contributory causes are, probably, (1) the secretions from the deposited ova, which are undoubtedly escaping continuously into the portal blood, and (2) the passive congestion produced in the liver by the embolic closure by eggs of many minute portal radicles. The finer interlobular cirrhosis and the larger scars, in extreme cases, are undoubtedly due primarily to the local effects of eggs deposited in the liver itself.

Histologically the liver in human cases shows all stages of the process of reaction to the eggs of the parasite. The predominating stage is that of repair, with the replacement of polynuclear leucocytes by mononuclears, and with the production of masses of scar tissue which may or may not be associated with recognizable portal spaces. In the scar tissue are eggs, often in large numbers (Fig. 38). As in the intestine the tubercle formation may be definite, and the eggs may be surrounded or invaded by foreign-body giant cells (Fig. 39). The liver tissue adjacent to scars may show some compression, emphasizing the productiveness of the inflammatory process, and accounting for the frequent enlargement of the organ, even in the late stage of the disease. The portal spaces which persist show marked thickening of connective tissue in which eggs may or may not be present (Fig. 40). This increase seems definitely out of proportion to the number of eggs locally deposited. Hematin deposit is more marked than in experimental dogs. The Küpffer cells often stand out as black masses.

Phagocytic cells in portal spaces are laden with small or large granules. In the "tubercles," especially at their periphery, such pigment-laden cells are often numerous. The liver cells themselves may be relatively normal in appearance, or they may show all degrees of fatty infiltration. This change is not at all proportional to the degree of infection and is probably only secondarily associated with the parasitic infection. Intense scarring of the organ may produce localized areas of typical chronic passive congestion, or of obstruction of bile capillaries. The liver capsule shows thickening by fibrous tissue in which may be many lymphocytes or other wandering cells, and occasionally large veins representing a collateral circulation (Fig. 41).

In summing up *the end result of S. japonicum infection upon the liver*, the condition *may be described as a portal cirrhosis associated with productive inflammatory foci leading to scar formation.* It is perhaps midway between the finely scarred hobnail liver of nodular cirrhosis and the coarsely scarred liver of syphilitic cirrhosis. In comparison with infection by *S. mansoni* the thickening of the portal veins is probably about equal in the two conditions, but there is a marked difference in the local effect of egg deposition. The greater egg producing power of *S. japonicum* results in a far more extensive closure of the interlobular portal veins, with a greater damage to liver function and much more obstruction to the gastro-intestinal and splenic circulation. For this reason the terminal picture of the two diseases, both clinically and anatomically, is a decided contrast. In *S. mansoni* infection the rectal symptoms predominate, while cirrhosis of the liver and enlargement of the spleen are noted as secondary phenomena. In schistosomiasis japonica, on the other hand, a massive ascites usually follows the cirrhosis, and the spleen is often hugely enlarged, so that the emaciated patient appears to consist mostly of abdomen.

The association of primary carcinoma of the liver with schistosomiasis japonica has been noted by Japanese writers (Kusama, 1907; Watanabe, 1912). Since the association of the two conditions is of rare occurrence, it would be difficult to establish a causal relationship between them.

Spleen. The most striking fact concerning the late pathology of this organ is its variation in size. This variation is not proportional to the intensity or duration of the disease. It is possible, however, that there may be, frequently, a rough inverse ratio between the size of the liver and that of the spleen. This has been suggested by our clinical observations and is borne out by two of our human necropsy cases. In the first the liver weighed 1420 gms., the spleen 1250 gms.

In the second the respective weights were 1943 and 464 gms. It is difficult to explain such an inverse ratio, but the progressive contraction of scar tissue about the portal veins of the liver, and especially thrombosis of the portal or splenic vein, may be factors in the enlargement of the spleen. In the two cases just mentioned, the large spleen was associated with thrombosis of the portal vein, whereas the small spleen was not. Thrombosis of the splenic vein has sometimes been found as the only apparent cause for massive enlargement of the spleen. On the other hand, in conditions like nodular cirrhosis of the liver and Banti's disease, in which some circulating toxin is apparently the damaging agent, the spleen often becomes greatly enlarged without thrombosis of the portal or splenic vein. It is therefore safe to assume that the toxins liberated by the adult worms and their deposited eggs play a part in the hypertrophy of the spleen.

The capsule of the spleen becomes thickened and may become attached to the surrounding structures by fibrous adhesions. The organ is firm and externally gray in color. The cut surface is flat and smooth, fibrous trabeculae are prominent, splenic corpuscles are inconspicuous and the color is reddish gray. There may be small white infarcts adjacent to the capsule, due to arterial occlusion, or irregular mottled red and white areas scattered through the tissue, apparently due to thrombosis of small veins.

Microscopic sections show a marked increase of fibrous tissue, both in the normal trabeculae and in the reticulum of the organ (Figs. 42 and 43). Venous sinuses have thick stiff walls and stand open, even if the blood has escaped. Splenic corpuscles are small, their central arteries have thickened walls, and the lymphoid tissue which remains is not active and is invaded by fibrous tissue. The pulp contains few wandering cells and these are mostly of the large mononuclear or macrophage type. Many of these cells, as well as the endothelial cells of the sinuses, contain hematin, often in large irregular masses. Occasionally eggs of the parasite are found. Their source is difficult to determine, although it is reasonable to suppose that worms might deposit eggs directly in this organ from the splenic veins.

Kidneys. No lesions have been found which are directly referable to *S. japonicum* infection. When the liver is infiltrated by fat, the cells of the kidney tubules usually share in this metabolic disturbance.

Among the other abdominal organs eggs have been found by various writers in the pancreas, adrenals, coeliac ganglia, uterus, ovaries and the outer coats of the bladder. In the pancreas eggs could be deposited directly by the worms, in the other organs it is probable that the eggs

either were carried by the lymph stream or were transferred from the peritoneal coat of the intestine by direct contact with surrounding structures. No eggs or worms have ever been described in the veins or inner coats of the bladder.

Lungs. Grossly these organs show no pathology related to this infection, and microscopic section often fails to reveal any lesions. Frequently, however, eggs are found in the interlobular septa, doubtless transported there through the pulmonary arteries. These ova may develop about themselves the typical abscess, tubercle and scar, which may invade the lung tissue to a slight extent. The source of these eggs is also difficult to determine, but the probability lies on the side of their having gained an hepatic vein in the liver, as the result of the breaking of an abscess into such a vein. As in the dogs, however, the possibility of a worm discharging eggs into a pelvic vein of the systemic circulation cannot be ignored. The involvement of these organs is, of course, insignificant, as compared with the lungs in cases of *S. hematobium* infection.

Brain. The presence of eggs of *S. japonicum* in the brain has long attracted special interest because of the possibility of their producing focal lesions which would give clinical symptoms. One of the first cases in which eggs were found was one of Jacksonian epilepsy (Yamagiwa, 1890). Houghton (1910) has also described a case in which he suspected that brain symptoms were due to egg deposits in that organ. These cases are, however, relatively rare. It is difficult to understand how any great number of eggs could break through the barrier of both liver and lungs to reach the arterial circulation and the brain. Even if eggs were deposited in the systemic veins of the pelvis, one barrier, the lungs, would have to be penetrated.

Heart. Eggs have occasionally been found in the heart muscle, but without the production of any functional disturbance of the organ.

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We wish to record our appreciation of the valuable assistance given us by Dr. B. C. Hou of the Department of Pathology, Shantung Christian University, in performing autopsies on some of our dogs; and by Dr. W. S. K'wei, of Peking, in examining many of our serial microscopic sections.

SUMMARY.

1. The development of the pathology of infection by *Schistosoma japonicum* is divided for convenience into three stages: (1) the stage of

invasion and maturation of the parasite, (2) the stage of egg deposition and extrusion, (3) the stage of tissue proliferation and repair.

2. The invading cercaria produces a tissue reaction in the skin of the host, visible externally as a minute red papule, and characterized histologically by edema, congestion and leucocytic infiltration in the corium of the skin.

3. In the passage of the young worm through the capillary network of the lung, and later through that of the alimentary tract and other organs, hemorrhage is the principal lesion produced. There may also be a leucocytic reaction about the worm, if it escapes into the tissues of an organ.

4. During the maturation of the parasite in the portal system no anatomical lesions are produced except in animals with overwhelming infections, when a necrosis of the liver parenchyma and a degeneration of the convoluted tubules of the kidneys is produced, apparently from toxins secreted by the worm.

5. The earliest deposition of eggs in the walls of the intestine was observed in a dog, killed twenty-eight days after infection. At this time practically no cellular reaction was found about the eggs and they were all still within blood capillaries.

6. From observation of the position of the worms and eggs in this dog, we conclude that the male and female worm advance *in copula* into the veins of the submucosa of the intestine, that the female projects her head farther into the venules of the submucosa, or even into capillaries of the mucosa, and discharges a large number of ova at one time, possibly as many as two hundred. These eggs are forced further forward into the capillaries of the mucosa, from which location they can gain the lumen of the intestine quickly and with little tissue destruction.

7. The development of the intestinal lesions in experimental dogs was followed up to the sixty-fifth day after infection. The cellular reaction which appears about the eggs, as the miracidia within them become mature, consists mainly of polymorphonuclear leucocytes, among which eosinophiles are prominent.

8. The abscesses thus formed rapidly spread to the muscular and serous coats, with the deposit of eggs in those localities.

9. With the breaking of the abscesses in the submucosa outward, by small openings into the mucosa and lumen, the glandular epithelium of the intestine proliferates downward into the abscess cavities and finally may line them completely. This is probably an important factor in the development of the intestinal papillomata, seen in late human cases of the disease.

10. By the sixty-fifth day scar tissue has already begun to invade and encapsulate the lesions in the intestinal wall.

11. The transportation of eggs into the liver leads to lesions similar to those of the intestine. The portal spaces, being the center of the lesions, are often totally destroyed.

12. By the fortieth day after infection pigment granules appear in the liver, phagocyted by the Küpffer cells and by macrophages in the portal spaces, and about the egg lesions. Microchemical tests have shown that this pigment, as well as that in the alimentary tract of adult worms is free from iron and may probably be viewed as hematin.

13. No diffuse cirrhosis of the liver was found in experimental dogs up to the one hundred nineteenth day after infection.

14. The spleen contained hematin by the fortieth day after infection, and by the sixty-third day showed definite increase of the splenic reticulum and diminution in the size and activity of the splenic corpuscles. Enlargement of the spleen was inconstant.

15. The pathology of the period of tissue proliferation and repair is limited to the study of human necropsy material. The essential features of the intestinal lesions are great thickening due to scar formation in all layers of the wall, the development of papillomata on the surface of the mucosa, and the shortening and thickening of the mesentery.

16. Thrombosis of the larger mesenteric and portal veins is frequently seen in late human cases.

17. The liver becomes cirrhotic, but not usually decreased in size. Beside the lesions produced by the local deposition of eggs, there is a general thickening of the walls of the portal veins, both large and small branches. This has been called by Symmers, "pipe-stem cirrhosis." The general picture of the liver is midway between that of nodular and syphilitic cirrhosis.

18. Hematin is also prominent in the liver and spleen of human cases.

19. The spleen varies greatly in size. It may be hugely hypertrophied. There seems to be a rough inverse ratio between the size of the liver and that of the spleen. The pathology of the spleen consists essentially of a marked increase of the fibrous reticulum, with loss of most of the pulp cells and diminution in size of the splenic corpuscles. There may be white infarcts due to arterial occlusion or irregular areas of necrosis due to venous thrombosis.

20. Eggs found in the spleen and pancreas may have been deposited

there directly by the worms. Those in other abdominal organs probably reached there either by the lymph stream or by adhesion to portions of intestines where eggs had been deposited.

21. The lung lesions are insignificant, as compared to those in *S. hematobium* infection. Eggs found in the lungs in *S. japonicum* infections probably reached there from the liver.

22. In rare cases eggs of *S. japonicum* may reach the brain and cause clinical symptoms such as Jacksonian epilepsy. The path by which the eggs reach the brain is difficult to determine.

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Explanation of figures.

(Plates XXII to XXXI.)

Fig. 1. Cercaria in corium of dog's skin, 15 hours after infection. Note leucocyte reaction in tissue. C = Cercaria. × 200.

Fig. 2. A section adjacent to that shown in Fig. 1, showing congestion of blood vessel and leucocytes adherent to blood vessel wall. × 235.

Fig. 3. Young *Schistosoma japonicum* in alveolar capillary of lung of mouse, three days after infection. × 600.

Fig. 4. Lung of mouse, three days after infection, showing congestion of alveolar capillaries, hemorrhage into alveoli, and perivascular edema with accumulation of leucocytes. × 160.

Fig. 5. Liver of hyperinfected dog, fourteen days after infection, showing central necrosis of liver lobule. × 110.

Fig. 6. Kidney of hyperinfected dog, fourteen days after infection, showing coagulative necrosis of convoluted tubules. × 85.

Fig. 7. Blood vessel extending from submucosa into mucosa, containing eggs at its peripheral end. Also note portion of female worm in larger vessel in submucosa. Jejunum of dog, 33 days after infection. × 43. F = Female worm.

Fig. 8. Blood vessel extending from submucosa into mucosa containing eggs in its mucosal branches, and showing fan-like distribution of eggs from a central point in the submucosa. Jejunum of dog, 33 days after infection. × 110.

FIG. 9. Two groups of eggs in the mucosa of dog's intestine, 40 days after infection. A = group of immature eggs. B = group of eggs containing mature miracidia. Giemsa Stain. × 60.

FIG. 10. Abscess in mucosa of dog's jejunum, twenty-eight days after infection. Note the absence of eggs in the abscess itself. × 43.

FIG. 11. Female worm, held in gynecophoral canal of male worm, extruding an egg from its uterus into vein, in subserous tissue of dog's small intestine, 40 days after infection. × 140. F = female worm. M = male worm. E = egg being extruded. T = testes.

FIG. 12. Cross section of jejunum of dog, 33 days after infection. Eggs are seen as black spots in mucosa and submucosa. Note small abscesses in mucosa. Four pairs of worms are present in vein of submucosa, and other pairs are in veins of serosa and mesentery. × 9.

FIG. 13. Abscess in muscularis of dog's small intestine, 40 days after infection. × 43.

FIG. 14. Cross section of small intestine of dog, 65 days after infection. Note abscesses in all coats of the wall, peritoneal adhesions, epithelial proliferation into abscesses of submucosa. × 10. A = abscess.

FIG. 15. Subperitoneal abscesses in intestine of dog, 65 days after infection. × 44.

FIG. 16. Productive peritonitis caused by abscess of muscularis breaking through to the serosa. Intestine of dog, 65 days after infection. × 44.

FIG. 17. Epithelial proliferation into submucosa in scar tissue. Note that below the proliferated epithelium is an abscess partly evacuated and containing blood. Intestine of dog, 65 days after infection. × 40.

FIG. 18. Abscess cavities in submucosa, entirely surrounded by epithelium. Intestine of dog, 65 days after infection. × 44.

FIG. 19. Another similar abscess, surrounded by epithelium. × 83.

FIG. 20. Epithelial proliferation into abscess cavity in submucosa. Note evacuation of abscess contents through epithelial channel. Intestine of dog, 65 days after infection. × 44.

FIG. 21. Epithelium in abscess cavity shown in Fig. 20. It tapers off from columnar to squamous along the wall of the abscess. × 185.

FIG. 22. Male and female worms in vein of serosa of dog's intestine, 33 days after infection. Note eggs crowded together in uterus of female worm, and other eggs already deposited in vein by another worm. × 100.

FIG. 23. Newly arrived eggs in portal vein of liver of dog, 40 days after infection. No reaction has yet taken place about them. × 170.

FIG. 24. Acute abscess about eggs in liver of dog, 40 days after infection. No remains of the portal space can be seen. × 83.

FIG. 25. Organizing abscess or "tubercle," with radial arrangement of cells about egg, in liver of dog, 40 days after infection. Note also granular pigment in cells at periphery of tubercle. × 170.

FIG. 26. Foreign-body giant cell in organizing "tubercle" in liver of dog, 65 days after infection. Note pigment in cells at periphery of "tubercle." × 280.

FIG. 27. Edema of portal space, with suggestion of increase of fibrous tissue. Liver of dog, 40 days after infection. × 170.

FIG. 28. Hematin in capillary endothelial cells of liver of dog, 40 days after infection. × 560.

Fig. 1

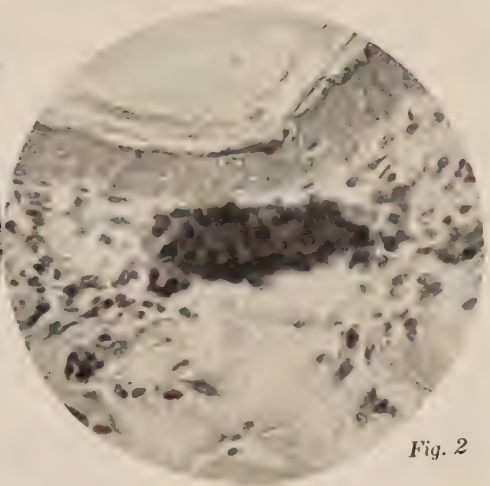
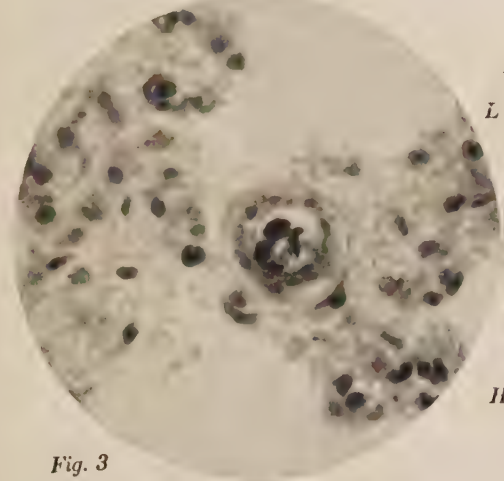


Fig. 2



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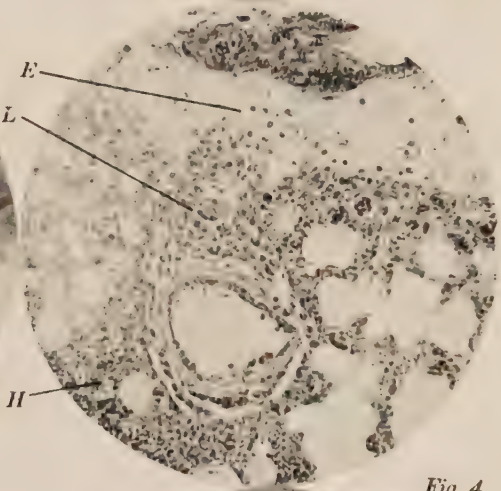

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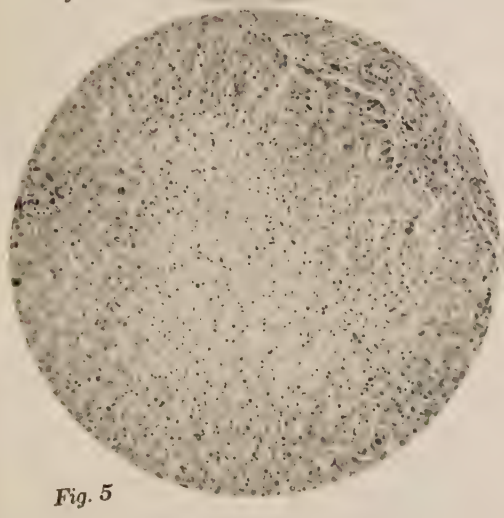

Fig. 5

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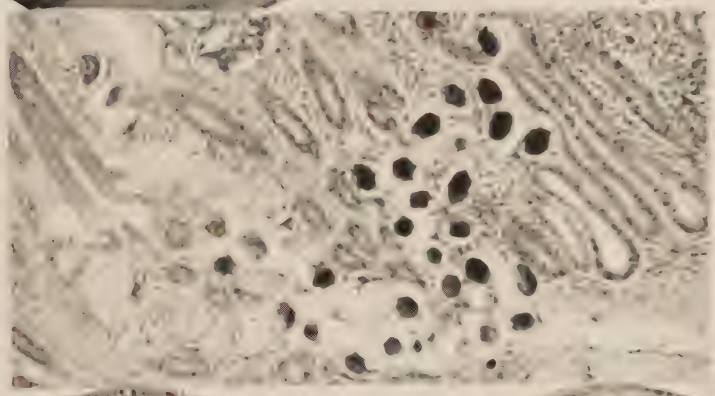
Fig. 7

Fig. 9



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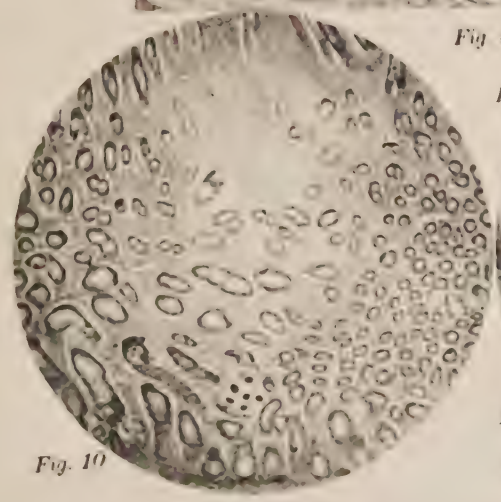

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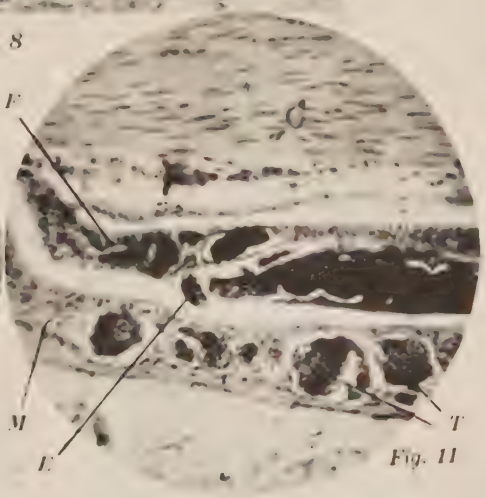

Fig. 11

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Fig. 12

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Fig. 14

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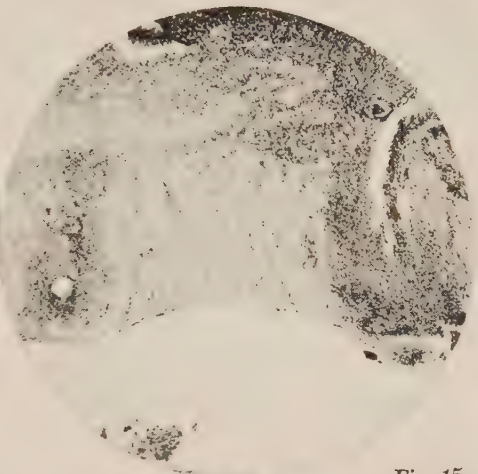
Fig. 13



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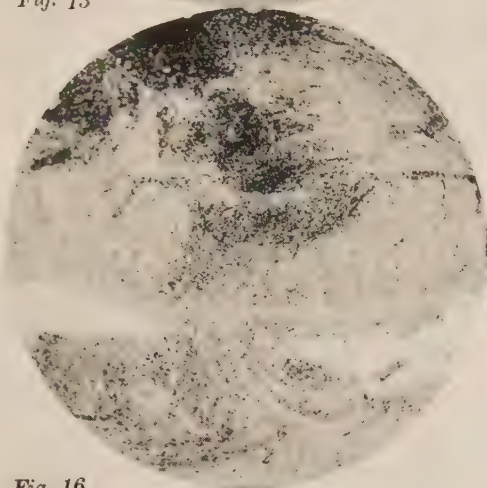

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Fig. 19

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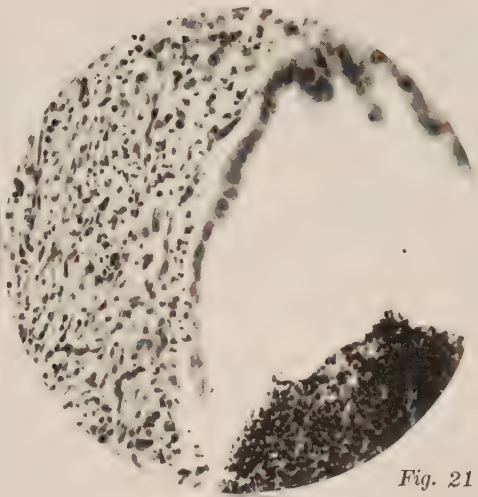
Fig. 20



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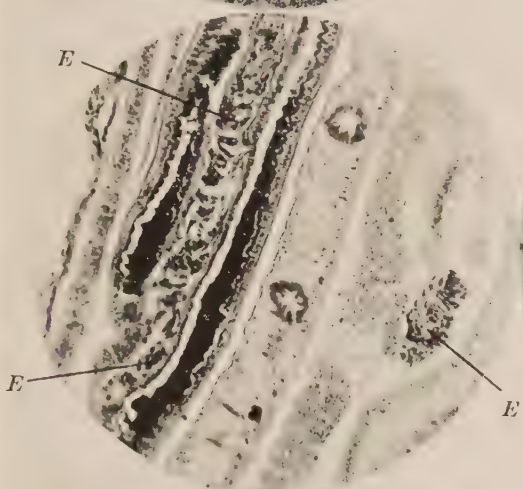
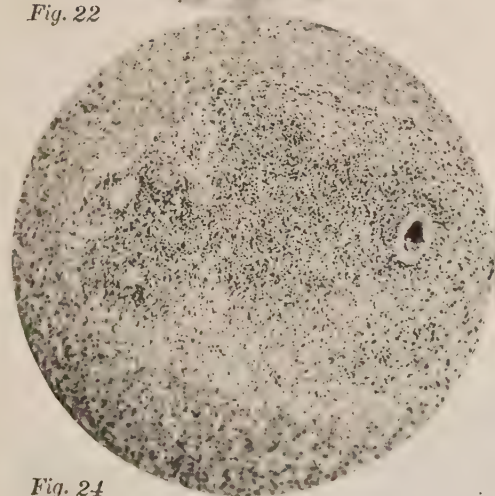


Fig. 22

Fig. 23



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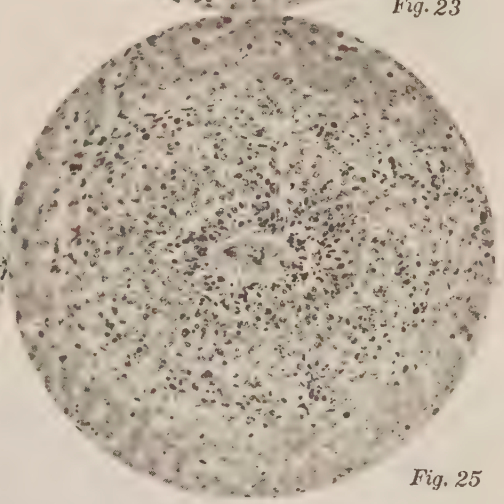

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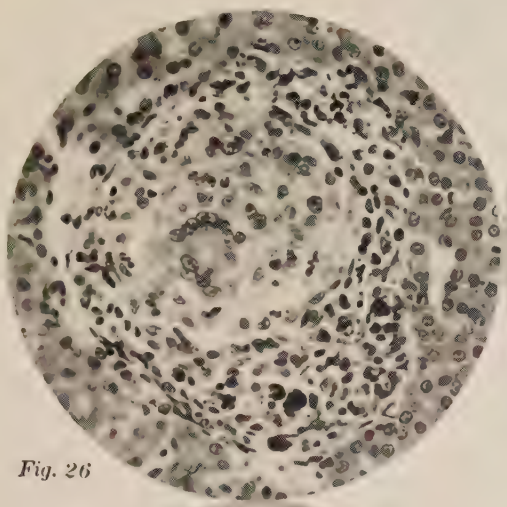

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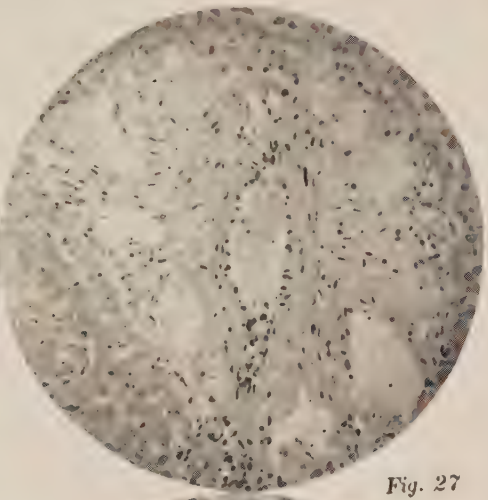
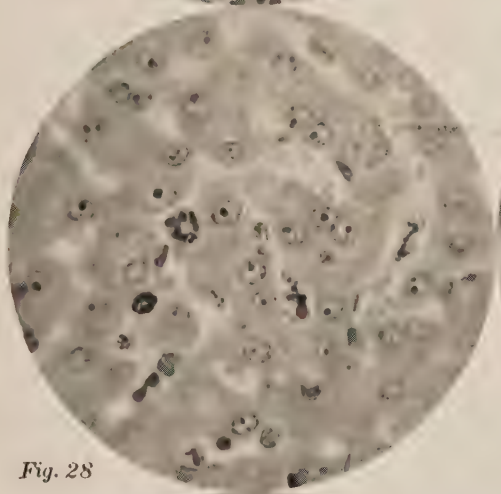


Fig. 27



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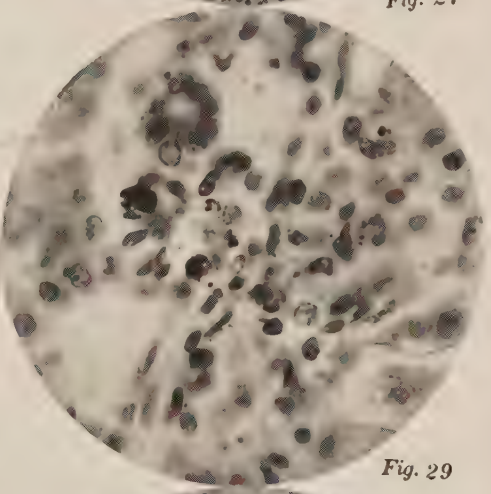

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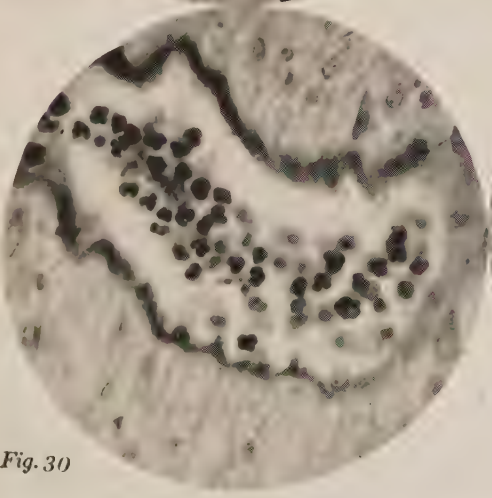

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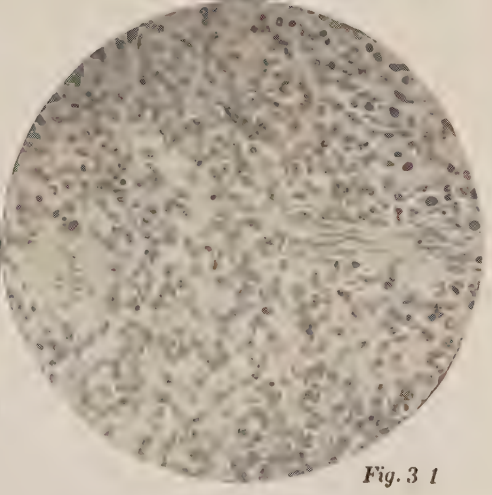

Fig. 31

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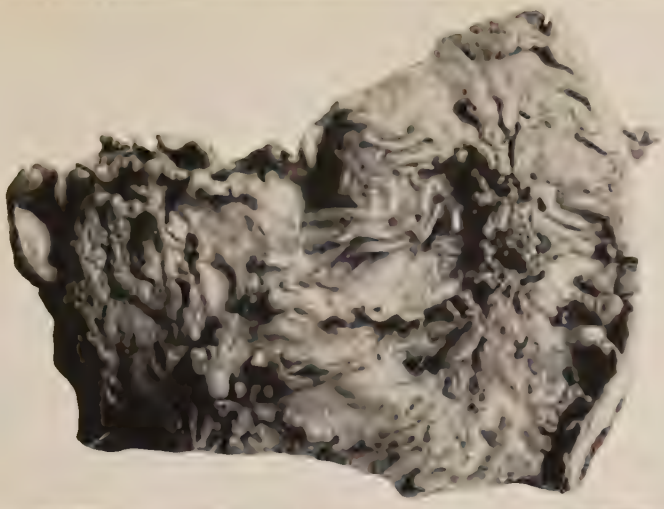

Fig. 32

Fig. 33

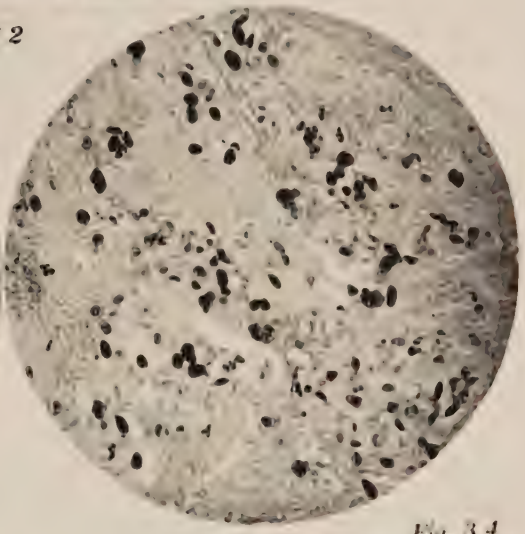

Fig. 34

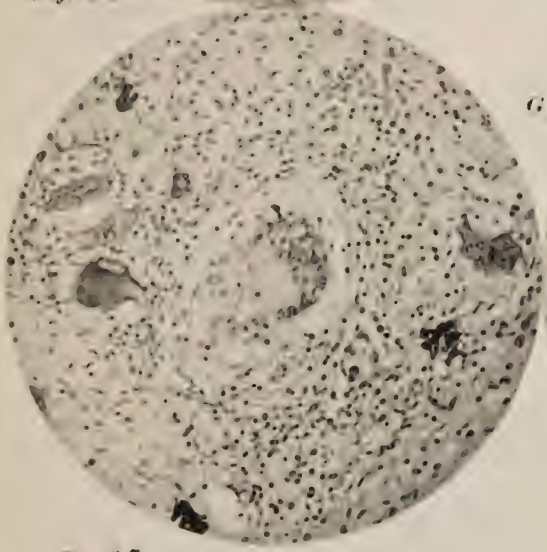

Fig. 35

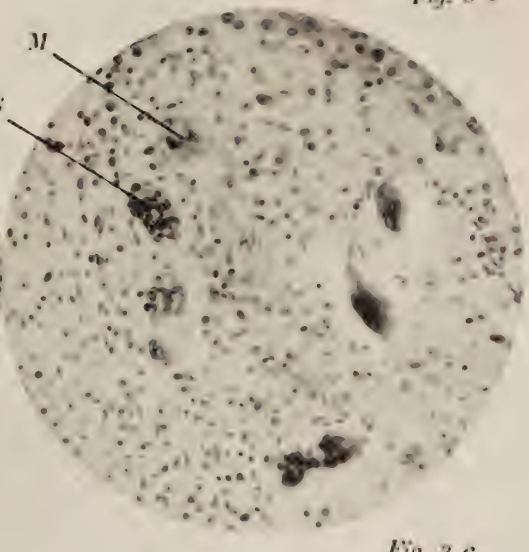

Fig. 36

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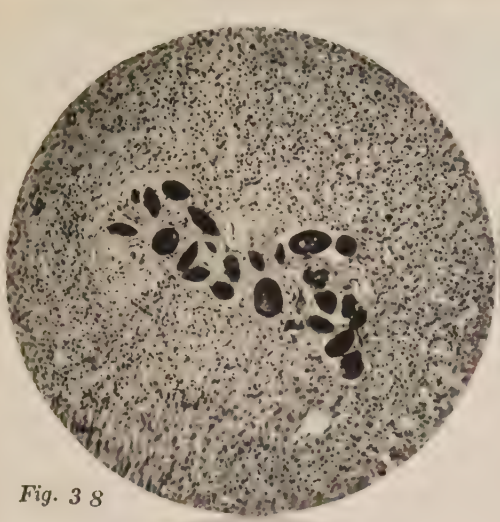


Fig. 3 8

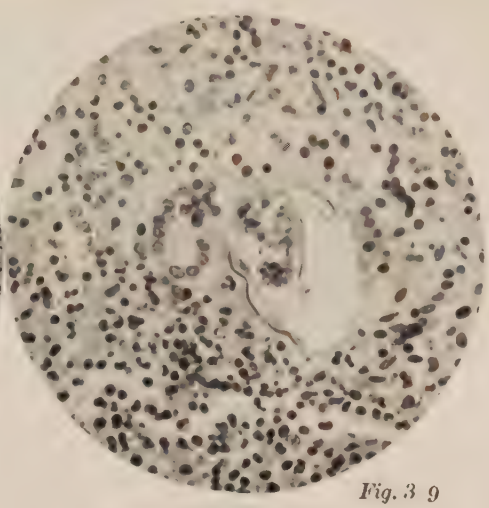
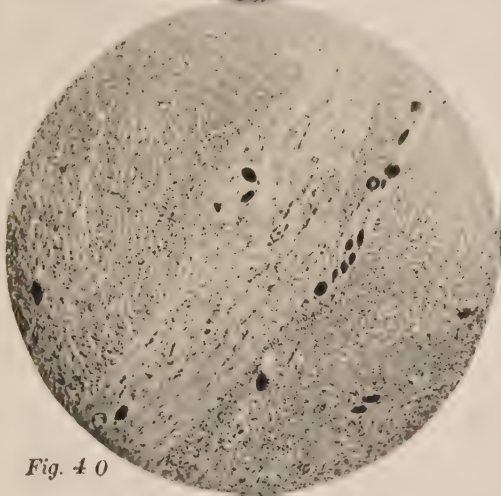


Fig. 3 9



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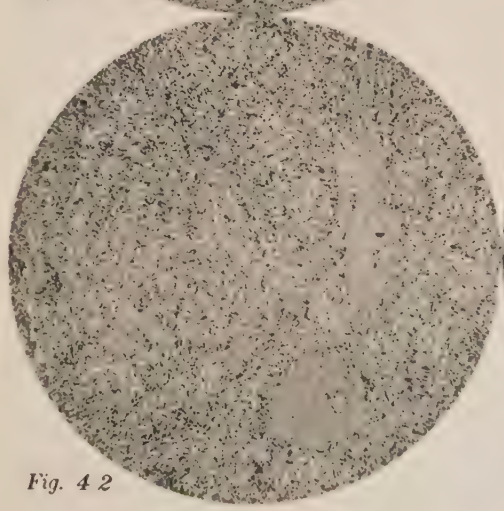

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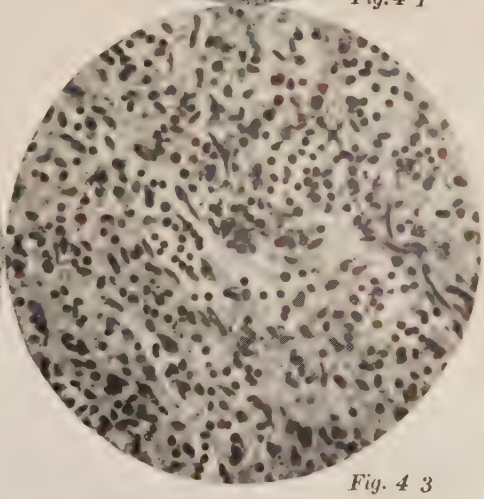


Fig. 4 3

(Faust and Meleney: Studies on Schistosomiasis Japonica, VI.)

FIG. 29. Hematin in phagocytic cells of an organizing "tubercle" in liver of dog, 74 days after infection. × 560.

FIG. 30. Well-preserved leucocytes in intestine of male worm. × 560.

FIG. 31. Spleen of dog, 63 days after infection, showing endothelial and fibroblastic proliferation in spleen pulp, and loss of wandering cells and blood. × 270.

FIG. 32. Mucous surface of the colon in a human case of schistosomiasis japonica, showing papillomata. × 1.

FIG. 33. Completely fibrosed "tubercle" in submucosa of colon, in a human case of schistosomiasis japonica. Note egg at center of "tubercle." × 80.

FIG. 34. Eggs of *Schistosoma japonicum* in scarred submucosa of human colon. × 38.

FIG. 35. Foreign-body giant cell in submucosa of colon; human case. × 160.

FIG. 36. Shell of egg of *Schistosoma japonicum*, invaded by foreign-body giant cell, in submucosa of colon; human case. Note contrast with adjacent egg which contains a miracidium. G = egg containing giant cell. M = egg containing miracidium. × 220.

FIG. 37. Cut surface of liver in a case of intense infection by *Schistosoma japonicum*. 3/5 natural size.

FIG. 38. Mass of eggs in liver; human case. × 86.

FIG. 39. Foreign-body giant cell "attacking" an egg in liver of human case. × 310.

FIG. 40. Thickened portal space in liver of human case, showing relatively minute blood vessels and bile ducts, and numerous eggs. × 41.

FIG. 41. Productive peri-hepatitis, with formation of large veins for collateral circulation; human case. × 42.

FIG. 42. Spleen of human case. Weight of organ 1250 gms. Note thick trabeculae, absence of splenic corpuscles and density of pulp. × 41. (Compare with Fig. 31.)

FIG. 43. Same spleen as Fig. 42. Note increase of fibrous reticulum, and hematin (?) pigment in phagocytic cells. × 270.

Note.—All figures except Nos. 32 and 37 are untouched photomicrographs of paraffin sections. Unless otherwise noted, they were stained with hematoxylin and eosin.

VII. CLINICAL SCHISTOSOMIASIS JAPONICA: CLINICAL AND LABORATORY FINDINGS AND SPECIFIC THERAPY.

(Plates XXXII and XXXIII; Textfig. 1.)

1. Introduction.

In describing the clinical picture of schistosomiasis japonica we present the results of our own observations of a rather limited number of cases, and also a resumé of the observations of many clinicians in China, and of Japanese workers, so far as the literature has been available to us. Our laboratory findings are based mainly upon the intensive study of seventeen cases of the disease at the Kashing Hospital, Chekiang Province, China, in June 1923. The specific therapy of the disease is still in its infancy, which makes it necessary to draw inferences from the methods used in the treatment of schistosomiasis hematobia and schistosomiasis mansoni. These are supplemented by out own experience and the few reports which are available from China.

2. Clinical findings.

The clinical course of schistosomiasis japonica is naturally divided into the same three stages* which we have previously adopted for the description of the pathology of the disease (Section VI, pp. 175 to 203). Since the explanation of the symptoms produced is based upon the pathological anatomy and physiology, we shall adopt here the same headings which we used in connection with the pathology, namely:

A. The stage of invasion and maturation of the parasite.
B. The stage of egg-deposition and extrusion (the stage of acute local symptoms).
C. The stage of tissue proliferation and repair (the stage of cirrhosis of the liver).

A. The stage of invasion and maturation of the parasite.

For the detailed description of this stage of the disease we are indebted to the physicians along the Yangtze Valley who had under their care Europeans and Americans who, as sportsmen or members

* These three stages of the disease correspond essentially with those given by Houghton (1923).

of crews of naval vessels, went into the lakes or canals in infected regions. The disease in its early stage was perhaps more carefully studied, because it was not recognized at first as being related to schistosomiasis, but was known as "Yangtze River fever," "Urticarial fever" or, by the sailors, "Blobby fever." The first published description of the disease in this stage was made by Lambert (1910) who recorded cases occurring in two British naval surgeons, three British naval seamen, and one British customs officer who was a keen sportsman. Contact with the water of rice fields or small streams or lakes was a constant point in the history of these cases, and this, together with the accompanying eosinophilia, made the first writers on the subject suspect an animal parasite as the cause of the disease.

The credit for the original suggestion that urticarial fever represented the stage of invasion of schistosomiasis japonica belongs to Dr. Henry S. Houghton, now director of the Peking Union Medical College, who was then a medical missionary at Wuhu on the Yangtze River. His suggestion was at once followed up by Lambert who found the ova of *Schistosoma japonicum* in the feces of his former patients, then in the second stage of the disease (Lambert 1911). Logan (1911), who had been the first to report clinical cases of schistosomiasis japonica in the Chinese, corroborated Lambert's findings in the case of an American boy who, in 1908, had had urticarial fever, then diagnosed as angioneurotic edema, and who, two years later was found to be infected with *Schistosoma japonicum*.

Two years after this Laning (1914), a medical officer on an American gun-boat, had seven cases of schistosomiasis among the crew of his ship, and, having a record of the exact location and activities of the men since their arrival in the Yangtze Valley, determined the apparent period of incubation from the time of infection to the onset of the early symptoms.

History and incubation period. The history is simple. It always includes evidence of contact with the water of rice fields, canals or lakes in regions endemic for schistosomiasis japonica, boys or sailors swimming in these waters, sportsmen hunting snipe or ducks through the wet country, sailors washing boats on the shore of lakes or washing down the decks of their ship with lake water when anchored close to the shore. Infection may occur at any season of the year which is warm enough for the active life of the intermediate host. In some regions, as in South China and some portions of the Yangtze Valley, this may be at any time of the year. In most of the Yangtze Valley and in Japan, however, infection during the winter is practically

impossible, and the months from May to October are the ones when most infections occur.

Itching of the skin over parts that have been immersed in infected water has frequently been reported by "foreign" patients in China and by Japanese writers. In China no definite skin eruption is known to follow infection. In Japan there is still a difference of opinion among investigators of the disease as to whether or not the skin disease, known as "Kabure," is produced by the invasion of the schistosome cercaria. We have previously discussed this point (Section VI, pp. 175 to 178) and agree with Miyagawa (1913) that the evidence seems to be definitely against any causal relationship between the two conditions. Careful examination of the skin of immersed parts, from twenty-four to seventy-two hours after infection, might reveal in human cases, however, as it did in one of our experimental dogs, a fine punctate eruption which represented the points of penetration of the cercariae.

The incubation period, according to Laning (1914), is from three to five days. His evidence is open to criticism, however, because of the fact that in two of his cases, eggs of *Schistosoma japonicum* were found in the feces at too early an interval, after the calculated date of infection, for the parasites to have reached maturity. His Case 2 showed eggs on the twelfth day, and Case 4 on the twenty-third day, after the supposed date of infection; while in his other cases eggs were not found at any time, at least until after his paper was written. In our experimental work, the twenty-seventh day is the first on which we have found eggs in the feces of dogs. It is probable that, in man, the period before egg extrusion is somewhat longer than this, since both worms and eggs have to travel farther than they do in a smaller host like the dog. It is probable, therefore, that, despite Laning's apparent control of the activities of the sailors on his ship, they became infected before the ship reached Tungt'ing Lake, possibly in the neighborhood of Shanghai, where cases are frequently encountered.

Laning is the only writer who has recorded such a short incubation period. Lambert (1911) states that the symptoms started in his case (Mr. A. M.) "some fifteen days after wading about the paddy fields." Logan's case bathed in infected water "when the weather became warm enough," but had no symptoms until a few days after July 4th, when he was at the hill resort of Kuling, where bathing is indulged in by foreigners without incurring infection. Our own case, an American naval officer, mentioned later in detail, had no symptoms whatsoever until the twenty-seventh or twenty-eighth day after infection. Fur-

thermore, in schistosomiasis hematobia and schistosomiasis mansoni symptoms similar to those about to be described have not been seen until the fourth to tenth week after infection (Lawton, 1917, 1918, Fairley, 1919*a*). We are compelled to conclude, therefore, that the incubation period of schistosomiasis japonica is not yet definitely established. The question deserves further careful observation.

Symptoms and physical signs. The earliest indication of illness is a general feeling of malaise toward evening, and the temperature, when taken, may be found to be from 38° to 39° C. This is soon followed in typical cases by pains in the back or leg muscles or along nerves, a dry, hacking cough, anorexia, possibly nausea and vomiting, a sense of abdominal distention, and occasionally diarrhea. The temperature falls nearly to normal each morning, associated often with profuse perspiration during the night, and rises again each evening to 38.5° or 39.5° C. The lungs show transient areas of dullness, associated with slight changes in breath and voice sounds and moist râles. These signs are remarkable for their variability from day to day, or even from hour to hour. There is occasionally a small amount of tenacious mucoid sputum.

The most remarkable physical sign, however, is an urticaria which is so intense, as to be accompanied by localized areas of edema, involving the subcutaneous tissues. It has sometimes been mistaken for angio-neurotic edema (Logan, 1911). The urticarial wheals vary in size from five millimeters to five centimeters or more in diameter. The wheals are raised, firm, white in color, round or irregular in shape, and are surrounded by a broad red areola which fades off into the surrounding skin. They occur on any part of the body, even on the penis and scrotum, and on the mucous membrane of the mouth. It is possible that they occur on all the mucous surfaces of the body and may be responsible for most of the early symptoms. The edema may consist of a small swelling beneath a patch of urticaria, or it may involve a whole hand or forearm, and eye, the pharynx, or the larynx. The eruption is accompanied, and often preceded, by intense itching of the skin. Scratching tends to bring out the lesions, which may thus be in the shape of long scratch marks or large irregular patches (as in our case). The itching disappears before the lesions, which fade from the center outward, their last evidence being a red ring enclosing normal skin. Dermatographia is usually present. The transient areas of lung dullness and the râles are easily explainable on the basis of localized edema of portions of those organs.

The following description of these early symptoms, given by Sur-

geon Gordon Moir of the British Navy, as observations on himself, shortly after infection, are so vivid as to deserve quotation. The notes were kindly placed at our disposal by Dr. A. C. Lambert:

" . . . I was quite well on the night of the 1st, but on getting up the next day I found that I had both wrists swollen and red, spreading for about 2 inches up the forearms. I was quite well during the forenoon, but about 3 P.M. I began to suffer from malaise. At 5 P.M. I had a distinct rigor: my temperature was then 102.8°(F). I took quinine sulphate, grs. xxx in three doses and turned in. Nov. 2d, temperature normal, no headache, and feel in all respects well. At 4 P.M. malaise again came on and at 5.30 another rigor started, lasting about 20 minutes. Temperature 101.6°. Nov. 3d, both wrists were greatly swollen, extending for about 2 inches up the forearms: the edges of the swelling were red, but the center was red (white?) and very irritating. This swelling disappeared about 1 P.M. Temperature was normal. At 5 P.M. another rigor started, lasting about 20 minutes: temperature 102°, half an hour after rigor, urticaria of buttocks and thighs commenced, each spot measuring about 2 inches across. During these two days quinine sulphate, grs. xx in two doses, was taken. Bowels regular. Nov. 4th, there was giant urticaria of the whole of the dorsum of left hand which disappeared about noon. . . . Nov. 5th, urticaria of the right hand similar to that of Nov. 4th. Nov. 6th. Urticaria of the back in large masses, varying from 2 to 4 inches across, rigor at 10 P.M., lasting about half an hour. Nov. 7th. . . . About 5 P.M. there was a profuse outbreak of urticaria over back and limbs. Nov. 8th. Urticaria of the upper lip which was enormously swollen, the left lower eyelid was also affected. This disappeared during the day. About 5 P.M. a rigor took place, lasting about 20 minutes, half an hour afterwards urticaria of the back and limbs came on. Blood count, eosinophiles 23 per cent. . . . Nov. 9th. Urticaria of both eyelids, left side and also over the malar bone on the right. . . . No rigor on this date; eosinophiles. 3 per cent. Nov. 10th. Urticaria of right upper eyelid and penis, disappeared by 10.30 A.M. No rigor. Eve. temp. 100°. Nov. 11th. Urticaria of uvula and right tonsil at 9 A.M., also of face over malar bone on the right side, this lasted till about 12 noon and then totally disappeared. Eosinophiles 18 per cent. . . . Nov. 13th. Urticaria of right eyelids at 9 A.M. disappearing about noon. . . . The spleen was found to be slightly enlarged. Nov. 14th. Urticaria of the trunk and limbs at 9 A.M. . . . After this date the pyrexia gradually ceased till on the 1st Dec. it was normal; the urticaria ceased completely. A recrudescence took place on the 21st Dec., when a temperature 101.2° was recorded, but there were no other symptoms and the general health was good. Still pyrexia lasted till the 4th Jan. and then completely finished."

The urticaria and associated edema are undoubtedly manifestations of the reaction of the human body to a foreign protein. The presence of the parasites within the blood easily accounts for the source of such a foreign protein, but the exact relation of the development of the worm to the phenomenon is less easy to explain. Not until the exact interval between the date of infection and the onset of the symptoms has been worked out, can we be sure whether the urticaria and edema are due to secretions from the worms themselves or from the eggs which the female worm deposits. The latter, we are sure, cause

most of the visible pathology of the disease. Some reports, like that of Lambert, quoted above, suggest that the symptoms are produced before the worms become mature, while others like our own American case, show no urticaria until after eggs have been found in the feces. The short duration of the foreign protein reaction, which is usually not over two weeks, may indicate either that the product of the worm, causing the phenomenon, has ceased to operate, or that the host's tissues have adjusted themselves to its presence.

Blood findings. The only blood examinations made during this stage of schistosomiasis japonica have been the estimation of hemoglobin and the enumeration of red and white blood cells. The red cells and hemoglobin are usually within normal limits, although there may be a slight decrease of both. The white blood cells are usually increased at first, reaching 10,000 to 12,000 per c.mm. Later they may be below normal. The eosinophiles vary from 5 to over 80 per cent. (one of Laning's cases), and there is a proportionate decrease of polymorphonuclears, the mononuclear cells remaining relatively normal. The eosinophilia is the most intense known for any disease.

Feces. In mild cases the first stage of the disease may be accompanied by no digestive disturbance whatsoever. In severer cases there is often an early diarrhea which may be a part of the systemic foreign protein reaction. On the other hand, the bowels may be constipated. Blood is never found in the feces during this stage of the disease, except in the most severe infections. As we have arbitrarily limited this stage to the period of the maturation of the parasite, there are, of course, no eggs of *Schistosoma japonicum* in the feces.

In Chinese patients, practically all of whom are ignorant peasants, the symptoms of the first stage of the disease have not been observed, so far as we can determine. There are two main reasons for this: first, these patients do not come to a "foreign" hospital until they are completely incapacitated for work, which is far beyond the first stage of the disease; second, because the symptoms of foreign protein intoxication, which make up much of the clinical picture in this stage, apparently occur only with the first infection, and are not seen after reinfections. Logan's case illustrates this. Urticaria and localized edema were seen in this boy during the first attack, but only fever and bloody stools were noted during the two subsequent years, after further bathing in supposedly infected water. Similarly Chinese patients, although they might be harboring worms in the maturing stage, would probably only show urticaria, if the observed attack was the first one, which is almost never the case. We have personally questioned late

cases of the disease among farmers and boatmen at Kashing, Chekiang Province, concerning symptoms prior to the first appearance of "bloody diarrhea," but have elicited no constant evidence of the urticaria, localized edema, cough or mild gastric complaints, described so accurately in "foreigners." In the presence of malaria, dysenteries and other infections, such details are difficult to elicit from ignorant patients.

The duration of the foreign-protein reaction, as judged by the persistence of urticaria and cough, is from one day to two weeks. The average duration is about five days. The fever, malaise and abdominal discomfort persist, however, for several weeks, and usually merge into the second stage of the disease. A typical chart of the course of the first stage of the disease is shown in Text-figure 1.

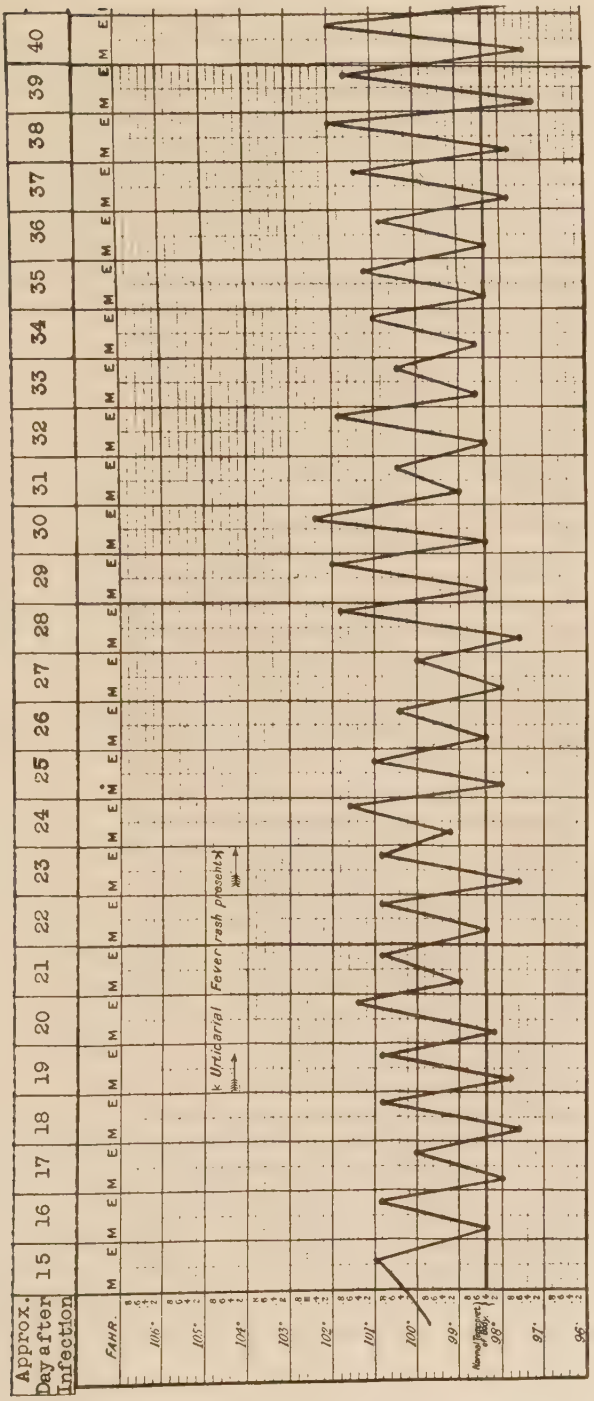
B. The stage of egg deposition and extrusion.

(The stage of acute local symptoms.)

The first stage of the disease usually passes imperceptibly into the second. Likewise the period of egg deposition merges with that of tissue repair; for the worms, particulraly in cases of reinfection, may continue their biological activity, even when the earlier lesions have produced a marked obstruction to the portal circulation, with cirrhosis of the liver.

The earliest symptoms of the second stage consist of a continuation of the earlier evening pyrexia, a malaise which simulates that of typhoid fever, and abdominal symptoms which vary greatly in intensity. Light cases often experience no abdominal disturbance except a vague feeling of distention in the epigastrium. This may be associated with slight tenderness in the liver region. The liver is slightly enlarged, though its edge may be difficult to palpate, and the enlargement seems to be more toward the mid-line than toward the right. The spleen also may be just palpable.

In cases of single infection the pyrexia and malaise persist for a variable period, from three to ten weeks. During this time there is considerable loss of weight (14 kg. in our case). The temperature falls by slow lysis to normal in untreated cases, and the patient slowly regains his strength, though he is liable to remain permanently below normal weight. If the case is undiagnosed before the patient's clinical recovery, it may remain a mystery unless some later incidental examination of the feces should reveal the schistosome eggs. In severe infections, however, and in cases of reinfection, the blood and mucus in the feces and the persistence of the debilitating pyrexia call further



TEXT-FIG. 1. Temperature chart of a case of "Urticarial Fever" beginning about 15 days after infection. Arrows show the duration of the urticarial eruption. (After Lambert, 1911.)

attention to the disease. Within a variable period the patient may notice a definite mass in the epigastrium or left hypochondrium, and the spleen may rapidly increase in size, until its margin reaches or even extends beyond the umbilicus. This may possibly occur within six or eight months after infection. On the other hand, there may be only slight enlargement of the spleen. The liver may enlarge enough to permit its palpation below the costal margin in the right flank, but more often its edge passes beneath the costal margin at about the midclavicular line. It may extend symmetrically below both sides of the costal arch, to within five centimeters of the umbilicus.

The enlargement of both the liver and spleen give prominence to the upper half of the abdomen. In extreme cases there may be a distinct fissure just above the level of the umbilicus, so that the contour of the abdomen suggests that of a somewhat distorted pear or gourd, turned upside down (Katsurada, 1905). This may be more noticeable in the early part of the third stage of the disease (Plate XXXII, Figs. 1–5).

The feces. In mild cases there is no diarrhea, and there may even be constipation. In severe cases there is a diarrhea in which the feces usually contain more or less blood and mucus. When very severe, the movements may be distinctly dysenteric, numbering ten to fifteen a day. Microscopically they consist of blood and mucus mixed with pus, thus resembling somewhat the stools of bacillary dysentery. In the mucus are the eggs of *Schistosoma japonicum*, often in large numbers. In mild cases the solid or soft fecal material may contain small particles of bloody mucus. It is characteristic to find the blood and mucus passed after the main portion of the stool and therefore on top of the deposited fecal mass. This is the typical schistosomiasis stool and persists, intermittently, as long as the worms continue to deposit eggs in the submucosa or mucosa of the intestine. Very mild cases may show no gross blood or mucus in the feces, and the eggs may be found only after careful search in the normal feces or after washing the whole specimen.

Method of examination of the feces for the eggs and miracidia of Schistosoma japonicum. It should be kept in mind that the shell of the schistosome egg is permeable to water, as well as to many salts in solution. Therefore the brine method of concentration of feces is unsatisfactory, for it shrinks the egg shell and miracidium into an unrecognizable mass. A direct smear of the feces, especially of a portion containing blood or mucus, should first be made. If eggs are not found by this method the following procedure has been found most

accurate in revealing the presence of eggs. The whole specimen of feces is worked through a wire mesh screen, to remove the larger particles of food material. It is then placed in a large glass container, of 1,000 to 2,000 c.c. capacity, and the container is filled with tap water. Distilled water should not be used, for its low specific gravity tends to swell the egg and at times kills the miracidium. The specimen is stirred vigorously to separate the soft particles of feces, and then is left undisturbed for about thirty minutes, allowing the sediment to settle. The supernatant fluid is then decanted off, down to the lighter portion of the sediment. The container is filled with tap water again, and the decanting is repeated until the supernatant fluid remains clear. The period of standing, before decanting, may be reduced gradually to fifteen minutes, and the specimen may be changed to a smaller container, as it becomes clearer. When the fluid is water-clear, after standing for ten minutes, portions of the sediment may be removed to fresh water, in a small Petri plate, and examined under the microscope for eggs. If this search fails, the whole sediment is left in its glass container in clear tap water for several hours, or overnight, at a temperature of 20° to 30° C. The next morning the supernatant fluid is searched carefully with a hand lens for miracidia, which appear against a dark background as minute, white, boat-shaped organisms swimming rapidly in a straight course. They are usually most numerous just below the surface pellicle of the water, but, especially if the water is a little cloudy, may be found in all layers of the fluid. In this way the presence of a very few eggs may be detected. The search for miracidia may be made easier by placing the washed specimen in an Erlenmeyer flask overnight. The small surface area tends thus to concentrate the miracidia. No suspected case of schistosomiasis should be declared negative until some such method has been tried. The method is also of value in determining the death of miracidia within eggs, and the disappearance of the eggs themselves, in cases under treatment.

The blood. With the progress of the disease there quickly develops an anemia of the secondary type. In mild cases it may be slight, in severe cases it rapidly becomes intense. An American under our care, seven weeks after infection, had 4,864,000 red blood cells per c.mm. and 83 per cent. of hemoglobin, while a Chinese with an infection of possibly only four month's standing, who was passing enormous numbers of eggs daily, had only 2,445,000 red blood cells per c.mm. and 23 per cent. of hemoglobin, (a hemoglobin index of 0.46). The white blood cells may or may not be increased. Our American case

had 17,680 white blood cells per c.mm., while the Chinese case mentioned above had 7,000. With the progressive anemia the white blood cells tend to become fewer, until a definite leucopenia may develop, even as low as 1,300 in late cases. In Chinese cases this is not constantly found, although a leucocytosis of 12,000 to 16,000 is sometimes present. Factors other than the schistosome infection may operate in debilitated Chinese patients to produce such a late leucocytosis. The eosinophiles may be tremendously increased. Our American case showed 39, 52, 45, 31, and 38 per cent. of eosinophiles at weekly intervals, beginning on the fifty-second day after infection. The Chinese case, just mentioned, showed, however, only 6 per cent. of eosinophiles. With the progress of the disease, the proportion of these cells becomes much more variable. In seven Chinese cases previous to the development of ascites they varied from 5 to 32 per cent. Except for the proportionate decrease of neutrophilic polymorphonuclear leucocytes, the other white blood cells show no significant changes. Other changes in the blood will be discussed later in presenting a series of Chinese cases together. Death from the disease in human cases during this stage rarely, if ever, occurs. So far as we know, no such cases have been reported.

C. The stage of tissue proliferation and repair.

(The stage of cirrhosis of the liver).

No cases of schistosomiasis japonica in Europeans or Americans have progressed, to our knowledge, as far as the third stage of the disease. Observations on the disease, in the period of cirrhosis of the liver, are limited, therefore, to cases among the natives of endemic regions, most of whom have been reinfected many times and represent a combination of the second and third stages of the disease. It is only in the most severe cases of single infection that sufficient scarring of the liver develops to produce the clinical picture of hepatic cirrhosis. There are cases, however, which do present the late picture of cirrhosis, whose infections took place so long before they came under observation that the worms have ceased depositing eggs, and have probably died. These cases are difficult to diagnose as schistosomiasis by the ordinary methods, since the most careful examination of the feces over a long period of time may fail to reveal any eggs of the parasite. Without serological methods, or perhaps even with such methods, these cases might remain diagnosed as cases of idiopathic cirrhosis of the liver. Necropsy, of course, can easily determine the correct diagnosis in such cases.

The typical late case of schistosomiasis japonica is, however, the one in which the picture of cirrhosis of the liver is combined with that of the second stage of the disease. *Emaciation* is often extreme, the skin clinging tightly to the contour of the bones, except for the abdomen which seems to be borne about by the patient as a tremendous burden (Plate XXXII. Fig. 1). The *ascites* is often extreme, or it may be relatively slight, and a huge spleen may give to the abdomen the inverted gourd appearance. The *face*, especially in adults, usually has the drawn, tired, dull appearance usually called "hepatic facies" (Plate XXXII, Fig. 2). It is often very pale.

In young patients, whose infection started during childhood, there may be great *retardation of development*, both physically and sexually, so that boys from seventeen to twenty-seven may appear to be five to ten years younger than they really are (Plate XXXII, Fig. 3). One girl of nineteen, married, was still preadolescent (Plate XXXII, Fig. 4). In contrast to this is the appearance of adults whose infection started too late to interfere with their maturity. They often appear ten years older than they are (Plate XXXII, Fig. 5.) *Weakness* is apparent by the manner in which they drag themselves about. General *pallor* of the skin is often extreme. In other cases there is a sub-icteric tinge to the skin and sclerae, though in orientals this is often difficult to distinguish from their normal complexion. In emaciated cases there may be patches of petechial hemorrhages on various portions of the body. *Dyspnea* on slight exertion is usually present, but most of the patients are not orthopneic, even when there is a marked ascites.

Atrophy of the muscles of the extremities is often extreme. There is rarely any marked edema of the legs or feet, such as one might expect with a massive ascites. *Dilatation of the veins* of the abdomen and thorax is often marked. The *teeth* of these patients are often remarkably well preserved. In a series of seventeen cases only four had any marked decay of teeth, and ten had no decay at all. In three of these seventeen patients there was marked atrophy of the papillae of the tongue, and in two others slight atrophy was present.

The *thorax* is cone-shaped, the atrophied muscles of the neck and shoulders accentuating this contour above, while the costal margin is expanded laterally to meet the distended abdomen. There is rarely any hydrothorax, and râles are heard only in extreme cases. The *heart* is often pushed upward. A functional heart murmur was present in ten of seventeen cases. The *blood pressure* is often far below normal. In one boy of 13 years it was, systolic 72, diastolic 52; in a man of 39 it was, systolic 82, diastolic 62.

Palpation of the *abdomen* reveals great variation in the size of the liver and spleen. Of twelve cases which had reached an advanced stage of the disease with or without ascites, the enlargement of liver and spleen varied as follows:

No.	Splenic enlargement.	Hepatic enlargement.
5	Marked	Slight
4	Slight	Marked
2	Marked	Marked
1	Slight	Slight

This suggests an inverse proportion, in many cases, between the size of the liver and that of the spleen. (Plate XXXIII, Fig. 6). This proportion does not vary with the degree of ascites nor with the apparent duration of the disease. We consider that it is probably related to thrombosis of the portal or splenic vein, and to a combination of other indefinite factors, including the toxemia of the infection and the early plugging of many portal venules by the eggs of the parasite.

Occasionally *masses of thickened omentum* or mesentery can be felt beneath the thin abdominal wall, particularly after the removal of ascitic fluid. In the removal of fluid such masses may obstruct the flow, and movement of the inserted cannula may detect hardened masses of tissue. In one case on which we performed a paracentesis practically no fluid could be obtained from below the level of the umbilicus, but 3500 c.c. were later removed by entering the cavity above the umbilicus (Plate XXXII, Fig. 1). This thickening of the mesentery, usually in its lower part, often binds the colon down in a firm mass, and emphasizes the "inverted gourd" appearance of the abdomen. When the ascites becomes extreme, however, the abdomen loses this contour and becomes almost hemispherical (Plate XXXII, Fig. 2).

The amount of *ascitic fluid* which can be removed is often less than in idiopathic cirrhosis of the liver, because of the inflammatory tissue within the abdomen. The maximum amount of fluid which we removed was 5400 c.c. The fluid may be clear or it may be cloudy or opalescent, suggesting the presence of chyle. The specific gravity ranged, in our cases, from 1.012 to 1.021 and the cells from 55 to 430 per c.mm. The cells were mostly mononuclears. The albumin content was relatively high.

Hemorrhoids are not as common as in idiopathic cirrhosis. *Hematemesis*, however, probably indicating varicose veins of the esophagus or stomach, occurred in three out of ten ascitic patients. Bovaird and

Cecil (1914) reported a case in a Japanese in which hematemesis was the immediate cause of death. The absence of hemorrhoids and rectal papillomata of large size is in striking contrast to the presence of these lesions in schistosomiasis mansoni, where they often form the predominating clinical feature of the disease.

Cases have been reported in which hemiplegia or Jacksonian epilepsy occurred, and, in some of the latter, eggs have been found in the brain at necropsy. This complication is apparently rare. We examined the deep and superficial reflexes carefully in seventeen cases without finding any definite abnormality.

The *temperature*, in patients who are suffering from two stages of the disease, usually continues the wide daily variation described as typical of the second stage of the disease. In six cases which were in the late ascitic stage, the average daily variation was 2.4° C., with an average maximum of 38.4° and an average minimum of 36.6° by rectum The pulse usually follows the temperature, having, in these same cases, an average maximum of 137 and an average minimum of 84.

The blood. The most striking feature of the blood count at this stage is the marked secondary anemia. Table 1, which will be discussed in detail later, shows the results of these examinations in seventeen patients. It will be seen that in the ascitic cases, the highest red blood count was 3,700,000 per c.mm., with the hemoglobin 47 per cent. This patient was a motor-boatman, who was going about his work daily. The lowest estimation was 1,460,000 red blood cells, with 10 per cent. of hemoglobin. The color index thus gave a maximum of 0.65 and a minimum of 0.36 in ascitic cases. The red blood cells showed central pallor, but no marked changes in size or shape. The white blood cells varied greatly in number: a leucopenia was encountered more often than a leucocytosis. The latter is probably the result of some secondary infection. The percentage of eosinophiles was, in general, much lower than in the first or second stage of the disease, varying from 0.3 to 19 per cent. Other blood findings will be discussed later.

The feces. A periodic diarrhea is common in these late, active cases. Houghton states that the feces of many late cases consist largely of undigested food. There may be occasional blood and mucus in the feces, but more commonly these are absent. Eggs of *Schistosoma japonicum* are almost constantly present in the feces, usually distributed evenly throughout the fecal material. The mode of living of these Chinese peasants is conducive to infection by intestinal parasites. Table 1 shows the presence of eggs of *Ancylostoma*, *Ascaris* and

TABLE 1.

Blood and feces studies on seventeen cases of schistosomiasis japonica from Kashing Hospital, Chekiang Province, China.

Case No.	Hosp. No.	Sex.	Age.	Stage of disease.	Blood.													Eggs of Feces			
					Million R.B.C.	Hemoglobin %.	Color index.	Thousand W.B.C.	Neutrophiles %.	Eosinophiles %.	Reticulated R.B.C. %.	Bleeding time; mins.	Coagulation time; mins.	Fragility of R.B.C.	Serum globulin test.	Aldehyde test.	Serum globulin %.	Wassermann.	Schistosoma Japonicum.	Ancylostoma.	Ascaris.	Trichuris.
1	475	F.	34	Quiescent	3.5	23	0.50	5.1	43.7	28	3.7	1.5	4	.35–.10	++	+	3.59	0	+	+	0	0
2	552	M.	34	Quiescent	4.4	48	0.55	6.4	51.3	22.3	–	1	–	–	–	+	4.48	0	+	0	+	0
3	2493	M.	13	Quiescent	4.0	51	0.65	7.2	45	32	–	2	–	.40–.00	+	+	4.84	0	+	0	0	0
4	415	M.	28	Early active	2.4	23	0.46	7.1	74	6.3	3.8	1.5	4.5	–	+	++	–	0	+	0	0	0
								4.5	85.5	1.5					++						
5	482	F.	30±	Mild active	3.2	38	0.61	10.4	71.3	4.7	–	–	3	–	0	+	4.92	0	+	–	–	–
6	443	M.	19±	Preascitic	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	0	0	0
7	447	M.	23±	Preascitic	3.1	27	0.45	1.4	57	7	0.5	–	6	.15–.05	+++	–	5.62	0	+	0	0	+
8	565	M.	40	Early ascitic	3.7	47	0.65	2.6	73	0.3	–	3	3.5	.35–.05	0	0	2.82	0	0†	0	+	+
9	564	M.	16	Early ascitic	1.5	10	0.36	16.0	82.3	1.3	–	2.5	6	.35–.05	++	++	5.17	0	+	+	+	0
								5.4	74	5.7					+++						
10	490	F.	45	Mod. ascitic	1.5	18	0.60	1.3	58	13	–	2	5	.30–.05	++	++	3.63	0	+	0	0	+
11	519	M.	27	Mod. ascitic	2.9	30	0.54	11.0	74.3	1	2.4	1	5	.32–.00	++	++++	7.65	0	+	+	0	0
12	478	M.	17	Late ascitic	3.1	32	0.50	9.2	51	19	2.3	–	–	–	++	–	–	–	+	0	0	0
13	479	M.	37	Late ascitic	3.5	38	0.54	5.5	79.3	3.3	–	1.5	5.5	.30–.10	0	–	7.96	0	+	+	+	+
									81.3	2.7					++						
14	480	M.	13	Late ascitic	1.9	20	0.50	9.8	88	2.7	3.0	–	5	.40–.10	++	–	5.33	0	+	+	0	+
15	537	M.	21	Late ascitic	3.1	34	0.57	12.9	83	0.7	4.9	2	4	.25–.05	++++	++	8.54	++	+	0	+	0
								5.4	75	3											
16	563	M.	39	Late ascitic	2.6	25	0.48	*16.0	93	0	–	–	5.5	–	++	++	5.62	0	+	+	+	+
								9.1	82.7	2											
17	571	M.	51	Late ascitic	2.6	40	0.77	1.6	81	5	–	1	5	–	+	+	4.62	0	+	0	+	0
Control (H.E.M.)												2	4.5	.40–.10	0							

Signs used. + = Positive with ++++ as the maximum. 0 = Negative. – = Test not performed.
* = Lip infected. † = Positive several months before; no symptoms at time of observation.

Trichuris in our series of cases. The presence of hookworm infection in these patients raised the question whether the marked secondary anemia could have been due to that rather than to schistosomiasis. Although it was probably a factor, analysis of our figures shows that even without it our cases suffered from a severe anemia. Table 2 shows the relation of anemia to hookworm infection in our series.

TABLE 2.

Relation of hookworm infection to anemia in patients with schistosomiasis.

	No. of cases.	Average R.B.C. per c.mm.	Average Hemoglobin per cent.	Average Color index.
With hookworm infection.....	6	2,600,000	25	0.49
Without hookworm infection....	9	3,100,000	36	0.58

The urine. No characteristic changes have been noted in the urine in any stage of *Schistosomiasis japonica.* In cases with marked ascites the volume of urine may be considerably diminished, and the specific gravity proportionately increased. In our series of seventeen cases a small amount of albumin was found in nine cases, but was not constantly present. Casts were found in only one case and were not constant. Bile and urobilin were never present. Diacetic acid was found inconstantly in three cases. Indican was constantly present in two cases and inconstantly in seven.

Prognosis. Since there is no multiplication of this parasite after its entry into the body of the final host, the severity of the disease in any one case depends entirely upon the number of cercariae which penetrate the skin. Therefore, mortality statistics, based upon the incidence of infection, which are reliable in bacterial and protozoan infections, where the parasite multiplies within the body of the host, cannot be applied to schistosomiasis. In cases which have been exposed to infection only once, the disease is rarely, if ever, fatal. Many such cases in Europeans and Americans, although untreated, have apparently recovered their health. Repeated reinfection is, therefore, the most important factor in prognosis. Among the native population of endemic areas the direct mortality from the disease depends upon the density of the snail population and upon the percentage of infection of the snails by the parasite. The percentage of infection of the snails depends, in turn, upon the number of infected persons in the neighborhood. In any community, therefore, the disease tends to propagate itself, producing more numerous and more heavily infected cases,—a vicious circle. In villages in which fifty to seventy per cent.

of the inhabitants are infected, which is common, it is safe to say that ten to twenty per cent. of them die of schistosomiasis.

Termination. The course of the disease in repeatedly infected cases, or in any case which develops marked ascites, is rapidly downhill. Abdominal paracentesis relieves the ascites only temporarily, and the toxemia of the infection, together with the loss of liver function, hastens the fatal outcome. Drug therapy is rarely of any avail in this stage of the disease. The lowered resistance, induced by the disease, encourages secondary infections like bronchopneumonia. Death may come apparently from exhaustion alone. The entire duration of the disease in fatal cases varies from one year (Tsuchiya, 1908) to many years. Probably some mild ascitic cases would go on indefinitely in the absence of secondary infection.

3. Special blood studies.

Through the cordial cooperation of Dr. F. R. Crawford and his staff at the Kashing Hospital, we were enabled to perform an intensive study of seventeen cases of schistosomiasis japonica in natives of that region, all farmers or boatmen. Table 1 shows the results of these examinations.

The blood cell counts and hemoglobin estimations have already been commented upon. In all these estimations the same red and white blood cell pipettes were used and the same closed, Thoma-Zeiss counting chamber. All were standardized and found to be accurate. For hemoglobin estimation a recently standardized Sahli instrument was used. In making differential white blood cell counts three hundred cells were always counted. The other results will now be dealt with individually.

Reticulated red blood cells. There was an almost constant, moderate increase in these cells in the seven cases examined, although it was not as great as might be expected from the degree of anemia present. One thousand cells were counted in each estimation, using a blood smear, stained vitally with dried brilliant cresyl blue.

The bleeding time was estimated by blotting the blood drop from a finger or ear stab every half minute after the puncture. A straight Hagedorn needle was used for the stab. The bleeding time in these cases was often shorter than normal and was never prolonged beyond the limit of normal.

The coagulation time was determined by using a glass tube 5 cm. long and 0.8 cm. in diameter, carefully washed with distilled water and rinsed with normal saline. Blood was withdrawn from a vein into

an all-glass syringe and was discharged immediately into the small tube, filling it one-third full. At intervals of thirty seconds the tube was carefully inverted and the coagulation time taken when the clot remained solid. It will be seen that the coagulation time in our series was always within normal limits.

Blood platelets. These were estimated roughly from their apparent number in the stained blood smears. There was great variation in the apparent number, without any definite relationship to other blood elements or to the bleeding time.

Fragility of the red blood cells. This test was carried out in the usual manner, using dried, chemically pure, sodium chloride, dissolved in double-distilled water, in dilutions of 0.025 per cent. gradation. In Table 1 the first figure represents the percentage of sodium chloride in which hemolysis began; while the second figure represents the percentage of sodium chloride in which complete hemolysis occurred. It will be noted that the fragility of the red blood cells was never greater than the normal control, and, in all but one of the ten cases tested, it was decreased.

The blood serum globulin. Brahmachari (1920) found that a white precipitate was formed by mixing the blood serum of a kala-azar patient with distilled water. He determined that this precipitate was a globulin-like substance,and considered the test valuable in the diagnosis of kala-azar, although a slightly similar reaction was occasionally found in chronic malaria. Ray (1921) made clinical use of the test by using a drop of the patient's blood. He made the mistake, however, of concluding that the precipitate was due to the presence of incompletely hemolyzed red blood cells. Sia and Wu (1921) have studied this phenomenon carefully and have shown that in the blood of active cases of kala-azar there is a marked increase, over the normal, of the total serum protein, as well as of serum globulin. In North China and in India, where schistosomiasis is not endemic, no disease, except kala-azar, has been found to give a strongly positive serum globulin test. The test is therefore used in Peking as a means of rapid, presumptive evidence of kala-azar. Paterson* and Libbey* have reported, however, that cases of schistosomiasis japonica give positive serum globulin precipitation tests. Since the endemic areas of kala-azar and schistosomiasis overlap at certain points along the Yangtze River, and since the cases of schistosomiasis with large spleens often

*Dr. J. L. H. Paterson of Tsaoshih, Hupeh Province, and Dr. W. E. Libbey of Wuhu, Anhwei Province. These reports were made in 1922, in answering a questionnaire on kala-azar, sent out by Dr. C. W. Young of the Peking Union Medical College.

closely resemble cases of kala-azar, it was important to study the reaction carefully in schistosomiasis.

We used a quantitative test, recently devised by Sia (1923), for estimating the intensity of the globulin precipitation reaction. In this test 20 c.mm. of the patient's blood, drawn into a Sahli hemoglobin pipette, is expelled into a small test tube containing 0.6 c.c. of distilled water. The tube is observed at once and, at intervals of fifteen minutes, up to one hour. An immediate clouding of the water indicates a positive test. Sedimentation of the flocculent precipitate within fifteen minutes indicates a ++++ reaction; sedimentation in thirty minutes indicates a +++ reaction; in forty-five minutes a ++ reaction; and in one hour or longer a + reaction. Table 1 shows the results of this test in 15 of the cases of our series. In another column are given the exact percentages of serum globulin in 14 cases. These estimations were kindly made for us by Dr. Hsien Wu by his own method (Wu, 1922). Sia and Wu (1921) found the average serum globulin in five normal cases to be 2.09 per cent., while in eight cases of kala-azar the average was 5.31 per cent. The average serum globulin in the 14 of our cases of schistosomiasis, in which it was estimated, was 5.34 per cent., which is practically equal to that in kala-azar. Another early case, an American naval officer gave a ++ positive reaction on the fifty-fifth day after infection, and the quantitative estimation of his serum globulin on that day was 3.68 per cent. A positive test and a high percentage of serum globulin may be obtained, therefore, both early and late in the diesase. As in kala-azar the degree of positive reaction is probably an index of the activity and intensity of the infection. In schistosomiasis, symptomless cases and late ascitic cases in which the worms are no longer active, might be expected to give only a slight, or a negative, reaction. The test has therefore not so great a practical diagnostic value in schistosomiasis, where a diagnosis can usually be made from stool examination, as in kala-azar, where the causative organism is often difficult to find. It will prove valuable, however, in estimating the efficacy of drug treatment in schistosomiasis, as it does in kala-azar, where a negative serum globulin test is now considered presumptive evidence of a cure. Although our findings should not lessen the use of this test in the diagnosis of kala-azar in areas not endemic for schistosomiasis, the test can no longer be considered a specific one for kala-azar, as Sia and Wu suggested, and in localities where both diseases are prevalent, it must be used with discrimination.

The blood serum aldehyde test. Napier (1922) and coincidently Fox

and Mackie (1921) described a test for the diagnosis of kala-azar, based upon the "formalin-jelly" test for syphilis, originated by Gaté and Papacosta. In some cases of syphilis the addition of a drop of 40 per cent. formaldehyde solution to 1 c.c. of blood serum causes the serum to coagulate into a stiff clear jelly. In all active cases of kala-azar Napier found that, in addition to the formation of a jelly, the serum became opaque and white. Less intense reactions produced an opalescence with diminution of transparency. Napier demonstrated that the opacity was produced by the globulin fraction of the serum. The test has proved practically pathognomonic for kala-azar in India. Tuberculosis and leprosy have been the only other diseases which have produced any opalescence of the serum, and these reactions have been faint.

We performed this test on the blood serum of 12 of our patients. In Table 1 the results are recorded according to the degree of opalescence or opacity produced, without regard to the formation of a jelly. In one case, No. 11, a stiff opaque jelly was produced within five minutes after setting up the test. This is recorded as $+++\dot{+}$. Five others showed moderate opalescence without opacity and are recorded as $++$. Slight opalescence in five other cases is recorded as $+$. Only one case was clearly negative, the serum remaining clear and producing no jelly. All the other sera produced a jelly, except No. 15. It will be seen that the results of this test correspond roughly both with those of the globulin precipitation test and with those of the percentage estimations of serum globulin. Since this test gives practically the same information as is furnished by the globulin precipitation test, which is much simpler to perform, it will probably never be used extensively.

The complement fixation test. Yoshimoto (1910) was the first to devise a complement fixation test for schistosomiasis. He used as antigen an alcoholic extract of adult specimens of *Schistosoma japonicum* and obtained uniformly successful results in Japanese cases of the disease. Fairley (1919) developed a similar test for the diagnosis of *S. hematobium* and *S. mansoni* infections, using as antigen an alcoholic extract of the livers of snails containing the cercariae of these parasites. More recently Le Bas (1922) has studied the reaction more carefully, and concludes that an aqueous extract of the infected snail livers gives the best results, and that a pure alcoholic extract does not contain the binding element. Both the Japanese and British workers claim value for the test in diagnosing obscure cases of the disease and in following the effects of drug treatment. The test has been per-

formed by Drs. C. W. Young and S. D. Joffick on several of the cases mentioned in this paper, and has proved to be specific in all cases where fresh serum was used. This work will be reported later.

The precipitin test. For practical purposes a test similar to the Sachs-Georgi test for syphilis, if proved to be reliable in schistosomiasis, would be of more value than the complement fixation test, in the hospitals of endemic regions in China, because of its relative simplicity. In collaboration with Drs. C. W. Young and S. D. Joffick, we have been attempting to develop such a test. The results of this work will be published in a later paper.

The Wassermann reaction. The Wassermann reaction was negative in 15 of the 16 cases in which it was performed. In one case a mildly positive reaction was obtained (++). This is considered as suggestive, but not as absolutely diagnostic of syphilis.

4. Differential diagnosis.

In the first stage of the disease the lung findings, together with the evening temperature and night sweats, strongly suggest acute pulmonary *tuberculosis*. In cases with unnoticed urticaria, *typhoid fever* may be suspected, the early bronchitis, the abdominal distress, the malaise and the diarrhea or constipation all simulating the picture of typhoid infection. Where the urticaria is marked, *food poisoning* or other *foreign protein intoxication*, or *angio-neurotic* edema may be suspected. The history of contact with water which possibly contained cercariae of *Schistosoma japonicum* should always make one suspicious of schistosomiasis, and the presence of a marked eosinophilia, which is almost invariably present, together with the history and any of the above symptoms, should practically settle the diagnosis. A positive complement fixation test is sometimes secured before the appearance of eggs in the feces and would aid in making a diagnosis. It may be that the globulin precipitation test will also prove valuable in diagnosing such early cases.

In the stage of egg extrusion the finding of eggs in the feces is practically always possible, if the search is made correctly. The presence of eggs in the feces is not sufficient, however, to eliminate other infections, which may coexist with an infection by *S. japonicum*. The bloody diarrhea of severe cases may simulate *dysentery*, the microscopic appearance of the stool suggesting that of bacillary rather than amebic infection. In milder cases, intestinal or miliary *tuberculosis* or *typhoid fever* may be suspected. Where the liver is enlarged and tender, amebic or other *abcess of the liver* must be excluded. With

a considerable enlargement of the spleen *kala-azar* is closely simulated and must be excluded by other tests than the globulin precipitation reaction.

The stage of cirrhosis of the liver offers difficulty in diagnosis mainly in those cases where no eggs can be found in the feces. In these cases *idiopathic hepatic cirrhosis* is the alternate diagnosis. Since that disease occurs frequently in China one would expect to find a certain number of cases in areas endemic for schistosomiasis. However, the occurrence of hepatic cirrhosis in a farmer or boatman, in an endemic area, is presumptive evidence in favor of schistosomiasis. The amount and character of the ascitic fluid may give some aid in the diagnosis. Syphilitic cirrhosis of the liver and *tuberculous peritonitis* with ascites may also resemble the late stage of schistosomiasis. The Wassermann reaction and guinea-pig inoculation of the ascitic fluid should aid in the differentiation of these conditions. Furthermore, in tuberculous peritonitis the ascitic fluid has more of the characteristics of an exudate, and has much less tendency to reaccumulate after removal.

5. Specific therapy.

The search for a drug with specific lethal action against the human schistosomes was unsuccessful for many years. Lambert, Logan and others in China found that, in the early stage before eggs appeared, quinine rapidly brought the temperature nearly to normal, and after prolonged use prevented a subsequent recurrence of the fever. Miyagawa (1912) was unable to make the eggs disappear entirely from the feces by the use of quinine, either in dogs or in one human case, although the eggs were reduced in number, the patient's symptoms improved and some "disintegrating" worms were found in the dogs at necropsy. Arsphenamin was used, both in Egypt and in China, with no apparent effect.

Diamantis (1918) first reported cures of *S. hematobium* infection in Egypt from the use of emetine. This has been followed up by several workers, and Cawston (1922) has reported its successful use in thirteen cases. Tyau* has used the drug in one case of schistosomiasis japonica with an apparent cure. Intravenous and subcutaneous treatment both appear to give satisfactory results. The initial dose is usually 0.03 gram (½ grain) a day, increasing as rapidly as toleration will permit, up to 0.13 gram (2 grains) daily. Treatment is given every day or three times a week. Vomiting is taken as the chief indication of the limit of tolerance. Cawston gave a single course of 1.2 grams

*Dr. E. S. Tyau, of Shanghai, China. Personal communication.

(18 grains) in 21 days to a patient 20 years old. Tyau suggests giving two courses of 1 gram (15 grains), each separated by an interval of one week. In his case the eggs of the parasite disappeared from the feces on the eighth day of treatment and symptomatic improvement was marked. This drug deserves more extensive trial in all three forms of schistosomiasis. It is easier to administer than the salts of antimony, and the danger of severe poisoning is less. The reports, so far published do not indicate that it is any less effective than antimony.

McDonagh (1918) was the first to report the use of antimony compounds in the treatment of schistosomiasis, but his work was not generally known and his cases were not followed to determine their ultimate cure. Christopherson (1918) independently started the use of tartar emetic (sodium or potassium antimony tartrate) in the Sudan in 1917, and demonstrated that the drug effected a permanent cure in both schistosomiasis hematobia and schistosomiasis mansoni. So successful has the treatment become in the hands of the workers in Africa, that large out-patient clinics are now established there, in some of which two hundred or more cases are treated each week. In schistosomiasis japonica, tartar emetic has also proved to be curative. Tyau (1922) has used it with success, and Tootell (1923) reports a series of 25 Chinese patients in which 12 were cured and one died of a complication, while failure in the other cases was stated to be due to their refusal to remain for the whole course of treatment.

The forms of antimony available for therapeutic use are as follows:

Sodium antimony tartrate, $2(NaSbO.C_4H_4O_6).H_2O$, (sodium tartar emetic). Less toxic and more soluble than the potassium salt; used in 1 per cent. or 2 per cent. solution.

Potassium antimony tartrate, $2(KSbO.C_4H_4O_6).H_2O$, (potassium tartar emetic). Most commonly used, because it is easiest to obtain; used in 1 per cent. or 2 per cent. solution.

Antimony sulphide, Sb_2S_3, in colloidal aqueous suspension, usually 0.2 per cent. Recommended by McDonagh, and used extensively in the treatment of kala-azar.

Potassium ammonium antimony tartrate $(KNH_4SbO)_2\ (C_4H_4O_6)_3 .2H_2O$. (Antiluetin). A commercial preparation advocated by McDonagh as being more efficacious than tartar emetic.

Of these compounds, the sodium and potassium antimony tartrates have been the only ones used on a large scale. As in kala-azar, they are administered only by the intravenous route. Administration by mouth is not effective, and in the subcutaneous tissues the drug produces necrosis. A one or two per cent. aqueous solution is used and

is prepared freshly every day. The sodium salt, being less toxic, is preferable to the potassium salt, but it is more difficult to obtain in chemically pure form. The routine followed by Christopherson is to begin with a dosage of 0.03 gm. (½ grain), and to increase by that amount in daily doses up to 0.16 gm. (2½ grains), unless a reaction is produced before that time. The interval is then changed to every other day, and the dosage kept at 0.13 to 0.16 gm. (2 to 2½ grains) until a total of 1.7 to 2.0 gm. (25 to 30 grains) have been given. This amount is usually sufficient for a cure in adult cases. Children are given proportionately smaller doses, the maximum dose usually being on the basis of 0.003 gram (3 mg.) per kilo of body weight.

Tootell used smaller doses than these in his series of cases. He began with 0.01 gm. (0.5 c.c. of a 2 per cent. solution) and increased by this amount in each subsequent dose up to 0.1 gm. He says he never dared give more than that amount, apparently because of the fear of having his patients refuse subsequent treatments.

Symptomatic improvement usually begins about one week after the treatment is started. In cases of schistosomiasis hematobia it consists in dimunution of the blood in the urine, relief of bladder and urethral pain and improvement of the general condition. In cases of schistosomiasis mansoni and japonica the blood in the feces becomes less, the temperature drops by lysis, and the asthenia and malaise disappear. In all types there is a diminution in the number of ova passed, and many of those passed fail to hatch, and are found, microscopically, to contain dead and disintegrating miracidia. In favorable cases the eggs usually disappear after ten to fifteen days of treatment. Christopherson states also that they turn black in color before their disappearance. In severe cases these dead eggs may be passed, at intervals, for weeks or months after the death of the worms themselves.

There is abundant evidence that antimony in therapeutic doses kills both the adult worm and the miracidium:

1. *In vitro* the worms are killed quickly by a concentration of the drug approximating that obtained in the blood. For the purpose of demonstrating this fact we performed the following experiment:

A dog just dead of *Schistosoma japonicum* infection was dissected, and many live worms were recovered from the portal and mesenteric veins. Thirteen dilutions of sodium antimony tartrate, dissolved in freshly obtained sheep serum, were made up, from 1–600 to 1–42,000. The solutions were placed in separate watch-glasses, and one male and one female worm were placed in each dish. The worms were then carefully watched under the microscope, at room temperature, and the

time noted at which all movement ceased. Death of the worms seemed to take place from the posterior extremity forward, as evidenced by a granular change of the body protoplasm developing into opacity. The ventral and oral suckers were the last organs to lose motility, hence the cessation of their motion was taken as the index of total death. Table 3 shows the time required to produce death by the various dilutions of the drug. It is impossible, of course, to estimate with any

TABLE 3.

The effect of sodium antimony tartrate on Schistosoma japonicum *in vitro.*

Solution No.	Dilution of S. A. T.	Time of death; male worms.	Time of death; female worms.
1	1 to 600	instantaneous	instantaneous
2	1 to 1200	1 min.	1 min.
3	1 to 1500	10 min.	10 min.
4	1 to 3000	10 min.	10 min.
5	1 to 4500	22 min.	32 min.
6	1 to 6000	25 min.	(injured) 25 min.
7	1 to 9000	26 min.	45 min.
8	1 to 12000	27 min.	35 min.
9	1 to 18000	(injured) 15 min.	36 min.
10	1 to 24000	30 min.	47 min.
11	1 to 30000	42 min.	59 min.
12	1 to 36000	51 min.	55 min.
13	1 to 42000	60 min.	60 min.
Control	0	44 hrs.	56 hrs.

degree of accuracy the concentration of the drug in the blood of a patient, on the basis of blood volume, because it is not known how much of the drug is absorbed from the blood by the tissues, or how quickly such absorption occurs. However, if we estimate the total blood volume as approximately 8.8 per cent. of the body weight (Keith, Rowntree, and Geraghty, 1915), or 88 c.c. of blood per kilo, and if the average maximum dose of the drug is considered to be 0.003 gm. per kilo, then the calculated concentration of the drug at the time of injection is approximately 1 to 29,000. It may be assumed, therefore, that a concentration of 1 to 42,000 would probably be exceeded for at least a short space of time after the administration of the drug, and the repeated use of such a dosage on consecutive or alternate days would soon kill the worms.

2. *In vivo,* clinical cures have been effected in all three types of schistosomiasis, and the cases have been followed for several years

without recurrence of the disease (Christopherson and Newlove, 1919; Christopherson, 1921). We have been able to cure two dogs of the disease and have proved the cure at necropsy.

3. The action on the miracidia is easily demonstrated by attempting to hatch them and by microscopic observation of the eggs.

The exact location where the antimony performs its action on the eggs is uncertain. Christopherson believes that the action takes place while the eggs are in the tissues. We believe, however, that there is more opportunity for the drug to act on the eggs after the latter reach the lumen of the intestine. It is known that a large proportion of the antimony is excreted by way of the intestine. This would probably produce a higher concentration of antimony in the lumen of the intestine than in the tissues outside the blood vessels. Furthermore we found that, if treatment was temporarily suspended shortly after the first failure of eggs to hatch, viable eggs could again be obtained in three days. Such a short period as this suggests that the lethal action took place mainly in the lumen of the gut. On the other hand, the excretion of dead eggs long after the cessation of successful treatment indicates that the drug also acts on the eggs in the tissues themselves.

We believe that the duration of a course of treatment by antimony tartrate may be shortened by starting with a larger dose than that advocated either by Christopherson or by Tootell. This is important in places where ignorant patients expect a rapid cure. If the dose is increased as rapidly as possible, up to the limit of tolerance, and if then the patient is kept saturated with the drug by doses just below that tolerance, until 1.5 to 2.0 grams (22½ to 30 grains) of the drug have been given, we believe that a successful course of treatment can be completed in about eighteen days. Theoretically this method is sound, because it should disable the parasite very shortly after treatment is started, and thus give greater chance for an ultimate cure in case the patient fails to remain for the full course. We recommend the following program of treatment:

Fresh solutions of the drug are made up each day in 10 c.c. of freshly distilled water. The total amount of solution is thus kept constant throughout the course of treatment, but the largest dose will not exceed a 2 per cent. solution. Treatments are given daily (midway between breakfast and lunch) in groups of three, each fourth day being a day of rest. The initial dose for an adult of 50 kg. (110 lbs.) weight is 0.05 gm. (¾ grain). Subsequent doses are increased by 0.025 gm. until a slight reaction is produced. This usually occurs with a dose

of 0.175 to 0.2 gram. Thereafter the dosage is kept just below the limit of tolerance, and the treatment is continued until about 1.5 gram of the drug has been given, or more (up to 2.0 grams), if the symptomatic improvement is very slow. A slight coughing at the end of the treatment should not be a contra-indication for continuing the treatment, but nausea, vomiting, dizziness, abdominal distress, diarrhea, or a marked rise in temperature, not due to the disease, should be followed by a day or two of rest and a slight reduction of the subsequent dosage. Such a course of treatment is ideal for early cases which are in good general condition. For very late or emaciated cases, with great destruction of liver tissue, a less intense program is safer.

In this connection the following case, recently under our care, is of interest:

R. H. G., age 33, American naval officer, went snipe shooting near Tungt'ing Lake, Hunan Province, China, on May 23 and 24, 1923. He wore shoes, socks, canvas puttees and woolen trousers, and waded freely in canals and ponds. He had no symptoms whatever until June 19, (twenty-seven days later), when he began to feel feverish at night, and had severe pains in the back and in the calf muscles. June 21 and 22, stool examinations (brine method) negative for parasites and ova. June 22, W. B. C. 8,100; eosinophiles 17 per cent. June 23, W.B.C. 9,200; eosinophiles 23 per cent. June 25. Temp. 101° F., constipated, had a constant feeling of fullness in the upper abdomen. After this the fever continued irregularly; weight became reduced from 130 to 115 lbs.; abdominal discomfort increased, constipation continued. Admitted to Peking Union Medical College Hospital on July 14.

Physical examination. Weight 114 lbs., appearance weak and depressed, skin sallow. Functional systolic heart murmur, liver dullness slightly increased in epigastrium, but edge not definitely felt. Slight epigastric distention and tenderness as well as constant distress. Spleen edge just palpable, hard and sharp, just below left costal margin, (history of malaria in youth). Temp. by mouth 37° C. at 12 noon, 39.2° C. at 8 P.M. Pulse 80–90, Resp. 20. Feces yellow, fluid (after catharsis). Eggs of *Schistosoma japonicum* found in fresh smear. R.B.C. 4,864,000. Hb. (Sahli) 83 per cent.; W.B.C. 17,680; neutrophiles 39 per cent., eosinophiles 38.7 per cent., lymphocytes 18 per cent., large mononuclears 3.7 per cent. Blood globulin precipitation test positive (2 plus). Urine normal. X-ray of lungs essentially negative. Treatment with sodium antimony tartrate (British Pharmacopoeia standard of purity) was started at once. A fresh solution of the drug was made up in 10 c.c. of freshly double-distilled water for each treatment. Treatments were given intravenously at 10 A.M., taking about 2 minutes to inject the 10 c.c. of fluid. Table 4 shows the schedule of treatments with their effect on the patient and on the eggs in the feces.

On the ninth day after starting treatment (63 days after infection) the patient was awakened in the night by intense itching of the skin. In the morning he found himself covered with urticarial wheals, each surrounded by a red-areola. Scratching the lesions caused them to develop into large irregular areas. They disappeared after two hours, but reappeared frequently, for a few hours at a time, during the next six days. There was no associated edema. We believed that this urticaria was due

to the schistosomiasis, but since it was relatively mild and was not associated with edema, and since some of our kala-azar patients who had been treated with the colloidal suspension of antimony sulphide had shown urticaria, we changed to Merck's chemically pure potassium antimony tartrate. Although the urticaria ceased on that day, we feel that it had simply run its course and that the drug had nothing to do with it. The patient's general condition improved rapidly during treatment, his malaise disappeared and he sat up for the greater part of every day during the last week of treatment. His weight decreased to 110 lbs. (a loss of 4 lbs. during treatment) A small amount of albumin appeared in the urine on the 10th, 11th and 18th day of treatment, but no casts were seen. Table 4 also shows the beneficial effect on the temperature, epigastric distress, total white blood cells, eosinophiles and serum globulin precipitation test. The patient was discharged twenty-two days after starting treatment, having regained two pounds in weight. Eighteen days after discharge he reported that he had gained ten pounds more in weight and was in excellent condition.

TABLE 4.

Intensive antimony tartrate treatment, Case R. H. G.

Day of treat.	Drug used.	Dose gms.	Total rec'd. gms.	Reaction.	Highest Temp. C. rectal.	Epigast. Distress.	S.J. eggs in feces	W. B. C. thous.	Eosin. %	Glob. ppt. test.
1	S.AT. (B.P.)	0.1	0.1	None	39.0	Moderate	+	16.0	52	++
2	"	0.1	0.2	None	38.8	Moderate	+			
3	"	0.1	0.3	None	39.2	Marked	+		45	
5	"	0.125	0.425	None	39.0	None	No feces			+
6	"	0.150	0.575	None	38.4	Slight	No feces			
7	"	0.175	0.750	None	38.2	Marked	+			
9	"	0.2	0.950	Cough, nausea after treatment	38.2	Moderate	+	7.4	31	+
11	"	0.175	1.125	Cough, felt weak after treatment	38.0	Slight	0			
14	P.A.T. (C.P.)	0.15	1.275	Slight cough	38.2	Slight	0			
15	"	0.175	1.450	Brief nausea	38.0	None	0			
16	"	0.175	1.625	None	37.9	None	0			
17	"	0.175	1.8	Nausea,cough, "all gone" feeling	37.4	Slight	0	8.1	38	±
21							0			
2 6								8.2	29	0

PRECAUTIONS.

1. Since antimony is poisonous and cases of hypersusceptibility have been reported, the first dose should be well below the probable point of tolerance. Death has been known to occur following a single dose of 0.1 gram of tartar emetic.

2. *Contraindications* for the use of antimony are: Nephritis, jaundice or other indication of acute liver disturbance, and myocardial weakness.

3. *Symptoms of poisoning.* The toxic symptoms met with, in their order of frequency are: (1) *cough,* (2) *nausea,* (3) *dizziness,* (4) *weakness,* (5) *vomiting.* These symptoms usually occur shortly after administration of the drug. The cough is apparently a local effect of bronchial irritation, and is not an indication for a change in the program of treatment. The other symptoms indicate that the limit of tolerance has been exceeded. Later toxic symptoms are (1) *epigastric distress* which usually comes on several hours after the earlier treatments and may be caused partly by the presence of eggs or of dead worms in the liver; (2) *rise of temperature,* usually occurring four to eight hours after treatment; (3) *diarrhea,* a severe effect of acute poisoning.

4. *Subcutaneous necrosis.* Antimony in the subcutaneous tissues is instantly and intensely painful, and may cause necrosis of the tissues, with thrombosis of adjacent veins. Such an accident is liable to destroy the confidence of the patient, which is a very important element in successful treatment. Extreme care must therefore be taken to introduce the drug only into the vein. The safest method is to draw a little normal saline or distilled water into the syringe just before introducing the needle. The needle should be long enough so that, after entering the vein, it may be pushed into the lumen a short distance to prevent its escape from the vein. A little blood should be drawn into the syringe to be sure that the needle is within the vein. The drug should be adiminstered very slowly, even though the patient may complain of local discomfort. Rapid administration is more likely to produce a reaction.

5. *Relation of treatment to meals and activity.* The most advantageous time for treatment is mid-way between meals, and the previous meal should be a light one. Treatment shortly after meals especially should be avoided. The patient should lie down for a short time (one half to one hour) after treatment, and should not over-exert himself or over-eat at any time during a course of treatment. The out-patient work in the Sudan has demonstrated that hospitalization is not necessary in carrying out a course of treatment. Intensive

courses of treatment, such as we have advocated, should be administered, however, only to hospital in-patients.

6. *Antimony preparation to be used.* The sodium salt is less toxic than the potassium salt, but a chemically pure preparation of the latter is preferable to a poorer grade of the former. Tablets of the drug, put up in combination with sodium chloride, do not give as good results as the fresh drug in powder form. *Solutions of the drug for use should be made up freshly each day,* using freshly distilled water. The solution should be sterilized by boiling for 1 to 5 minutes. Prolonged sterilization under pressure or old solutions are thought to produce more reaction in the patient.

Schistosomiasis and Kala-azar.

It is noteworthy, and is perhaps of some biological importance, that the two diseases in which antimony has proved to be of the most value in treatment, are also the only two in which marked increase in the blood serum globulin has thus far been found. These facts are especially interesting, because the organisms causing the disease are quite different in systematic position, one being a metazoon, the other a protozoon. They have the common habitat of the blood stream, however, which is of great significance, and the pathology which they produce, especially the anemia and the splenomegaly, have points in common. This is not the place to go further into the discussion of these phenomena, but the study of parasitic diseases from the point of view of their common effects on the host's tissues and their susceptibility to a common poison may, in the future, lead to a better understanding of their biological relationships. The human trypanosomes, which hold a close systematic relationship to the Leishman-Donovan body of kala-azar, and which are said to be susceptible to antimony treatment, may also be found to produce a high blood-serum globulin in the human subject. Such a finding would further emphasize the biological importance of these common phenomena.

Acknowledgment.

It is a pleasure to express our appreciation to Dr. F. R. Crawford and the entire staff of the Kashing Hospital for their cordial cooperation in the study of clinical cases; to Dr. A. C. Lambert of Chiao Tso, Honan Province, China, for permission to use his notes on cases of "Urticarial fever"; to Dr. Hsien Wu for the performance of the quantitative serum globulin determinations; and to Dr. Charles W. Young for assistance and advice on many phases of this work.

Summary.

1. The clinical course of schistosomiasis japonica, like the pathological, may be divided into three stages: (1) the stage of invasion and maturation of the parasite; (2) the stage of deposition and extrusion of eggs; and (3) the stage of tissue reaction and repair.

2. The first stage of the disease is characterized by fever, malaise, cough, giant urticaria with edema, intense eosinophilia and occasional abdominal symptoms.

3. The second stage is characterized by blood and mucus in the feces, with or without diarrhea, and by the continuation of fever and malaise, associated with epigastric pain. Eggs of the parasite are almost constantly found in the feces. The liver and spleen become enlarged, the latter often to a massive size. A progressive anemia develops, while the eosinophilia is varied in degree.

4. The third stage is characterized by symptoms of cirrhosis of the liver and portal obstruction. Emaciation often becomes extreme. In most cases frequent reinfection combines this picture with that of the second stage.

5. An accurate method is described for examining feces for eggs of *Schistosoma japonicum* and for following the death of miracidia within the eggs during treatment.

6. The blood-serum globulin is increased in this disease to an average of more than twice the normal. It is as high as that found in kala-azar. The "globulin precipitation test" and the "aldehyde test," which previously had likewise been considered to be specific for kala-azar, were found to be strongly positive in many cases of schistosomiasis.

7. Other blood tests done on a series of 17 patients, showed the changes which would be expected with the anemia produced by the disease.

8. The anemia found in schistosomiasis japonica is entirely independent of hookworm infection, although it may be somewhat increased by that complication.

9. Emetine and preparations of antimony have been found to have specific lethal action against all three types of human schistosome. Emetine has not been sufficiently used in schistosomiasis japonica to warrant sweeping claims. Antimony, however, usually employed in the form of sodium or potassium antimony tartrate (tartar emetic), has produced cures in all three stages of the infection.

10. We advocate, with the use of proper precautions, an intensive course of treatment, in which the patient's tolerance for the drug is

quickly reached; treatments should be given as frequently as tolerance will permit. In this way a total of 1.5 to 2.0 grams of the drug can be given in 18 or 20 days to an adult not too far advanced in the disease.

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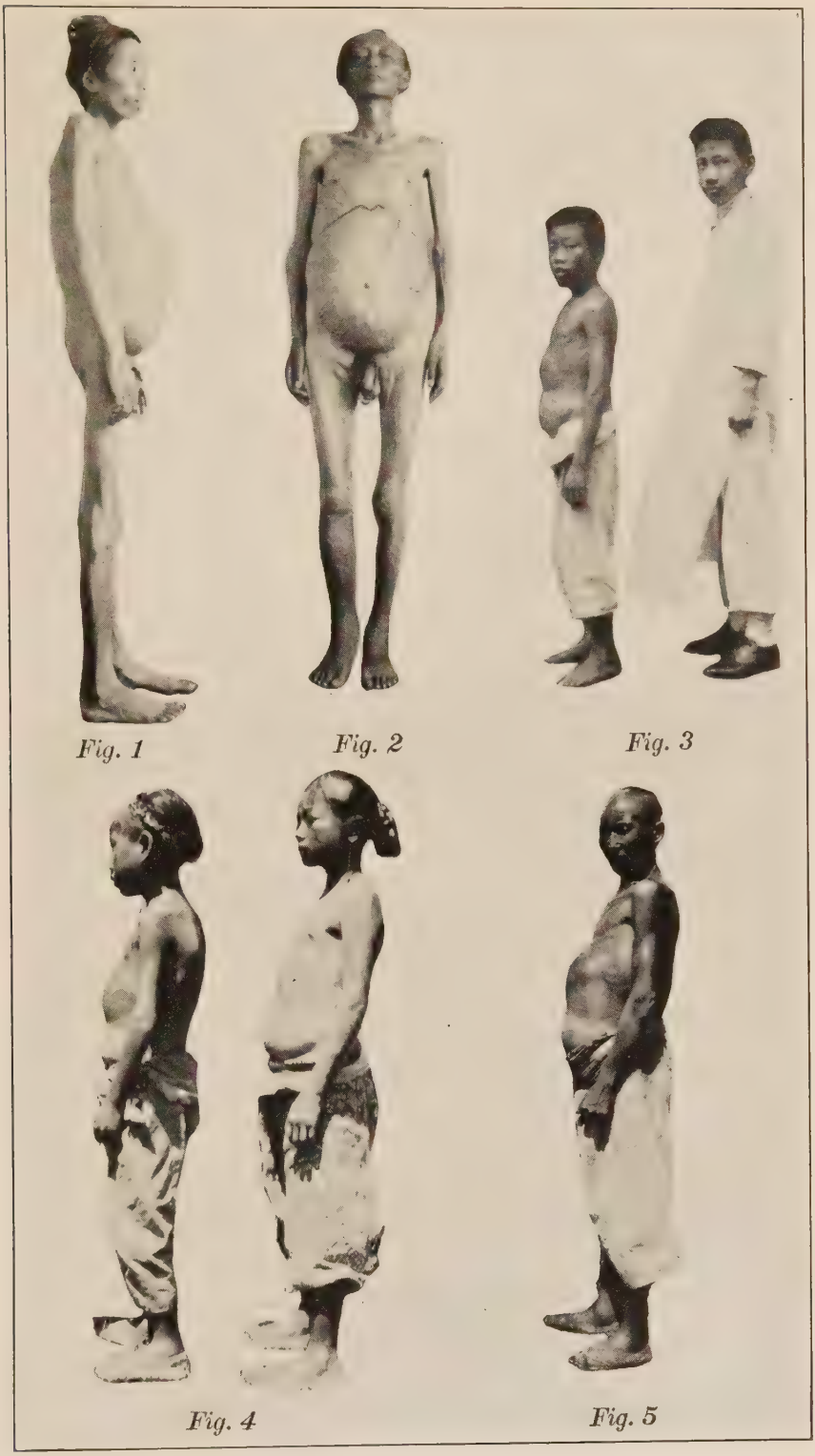

Fig. 1 *Fig. 2* *Fig. 3*

Fig. 4 *Fig. 5*

(Faust and Meleney: Studies on Schistosomiasis Japonica, VII.)

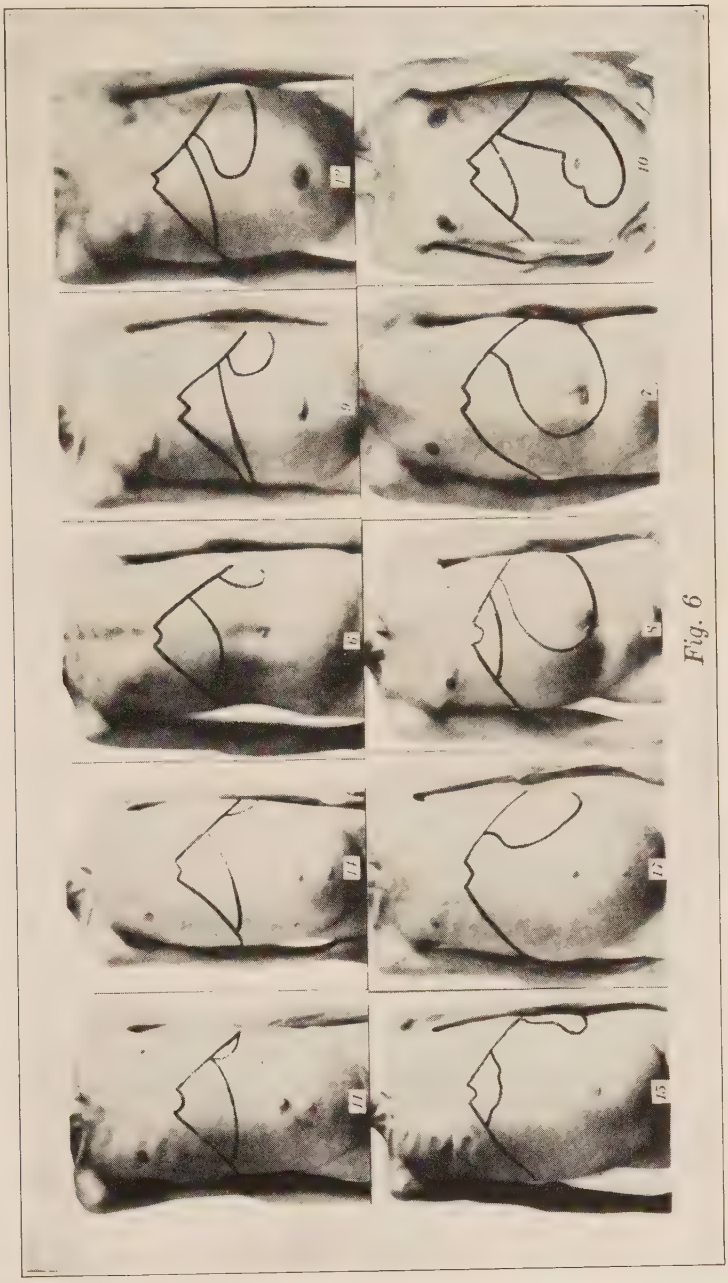

Fig. 6

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Explanation of figures.

(Plates XXXII and XXXIII.)

Fig. 1. A late case of schistosomiasis japonica, Kashing, aged 21, showing intense emaciation and ascites. The photograph was taken after 3800 c.c. of fluid had been removed from the abdominal cavity. No fluid could be obtained from a puncture below the umbilicus. Note tendency to constriction in midabdomen.

FIG. 2. A late case of schistosomiasis japonica in an adult, Kashing, showing the "hepatic facies" and marked ascites.

FIG. 3. A case of schistosomiasis japonica from Soochow, aged 19, standing by a normal man of 20, emphasizing the stunting of growth caused by the disease. This case shows the typical "inverted gourd" appearance of the abdomen.

FIG. 4. A girl of nineteen (right) and a boy of fourteen (left), both suffering from schistosomiasis japonica. Both are stunted in physical growth and are sexually preadolescent. (Soochow cases.)

FIG. 5. A late case from Soochow, aged 41, emphasizing the appearance of old age in cases developing after maturity.

FIG. 6. Ten cases of schistosomiasis japonica from Kashing, showing the inverse proportion in size between liver and spleen. Numbers refer to case numbers in Table 2. The liver and spleen were outlined on each patient before photographing, and the outlines intensified on the prints.

VIII. PROPHYLACTIC ASPECTS OF SCHISTOSOMIASIS JAPONICA.

(Plates XXXIV and XXXV.)

Introduction.

In the preceding sections of this monograph we have presented data on the biological, epidemiological, pathological and therapeutic aspects of schistosomiasis japonica. We believe that the study has been fully justified, and that the knowledge which we now possess constitutes an entering wedge in attacking the problem of schistosomiasis japonica in China. While the magnitude of the problem of eradicating the disease from China makes it imperative that this work be initiated at the earliest possible moment, it is necessary first of all to consider briefly the possible lines of approach to prophylactic work in this disease, as well as the success or failure that has attended the preventive aspects of schistosomiasis japonica in Japan and bilharziosis in Egypt. The problem of schistosomiasis prophylaxis, as it appeared ten years ago and as it exists today, is comparable to the yellow fever situation of a quarter of a century ago and today. This has been admirably portrayed in the remarks of Professor Ashworth (1923) in his recent address before the British Association for the Advancement of Science.

"If we desire an illustration of the vast difference between knowing and not knowing how a disease germ is transmitted to man, we may turn to the case of yellow fever. When this pestilence came from the unknown, and no one knew how to check it, its appearance in a community gave rise to extreme despair and in many cases was the signal for wholesale migration of those inhabitants who could leave the place. But, with the discovery that *Stegomyia* was the transmitting agent, all this was changed. The municipality or district took steps to organize its preventive defenses against a now tangible enemy, and the successful issue of these efforts, with the consequent great saving of life and reduction of human suffering . . . is now common knowledge. . . . The campaign against Stegomyia is resulting . . . in yellow fever being restricted to rapidly diminishing isolated areas, and this disease seems to be one which by persistent effort can be brought completely under control."

Yet in many respects the problem for China is different and in many respects much more difficult of solution than yellow fever prevention.

Possible methods of approach.

There are four periods in the life cycle of *Schistosoma japonicum* when the parasite can be attacked. These periods and the methods by which the attack can be brought about are as follows:

1. *The adult worm and the egg in the mammalian host.*

a. In man. Specific treatment for the infection by potent drugs is the single effective method available during this period for man. Such drugs are known and can be used on a large scale with success. The limitations of this method lie, first, in the necessity for a long course of treatment, with possible toxic effects on the host, and, second, in the fact that usually lightly infected cases either do not seek treatment or escape diagnosis. Cases showing severe clinical symptoms are mostly those that have been exposed to the infection time after time.

b. In connection with human therapeutic prophylaxis the *elimination and exclusion from endemic areas of other mammals which serve as reservoir hosts* of the parasite constitute the only method of permanently reducing the adult worms and eggs in those areas.

2. *The extra-mammalian forms of the parasite.* This period includes the evacuated eggs and their miracidia, the sporocysts in the intermediate host, and the liberated cercariae.

a. The eggs and miracidia after evacuation from the mammalian host. This constitutes essentially a problem of the control of feces disposal. Since human feces are, in the present economic system of the Chinese, absolutely necessary to the successful fertilization of arable lands, the problem has an important economic aspect. Successful methods should, if possible, bring some positive, tangible benefit, or at least no detriment to the people upon whom limitations are placed. The restriction of promiscuous defecation is one important element in the problem, and must be emphasized in any efforts which are made. But far greater in importance is the requirement of destroying the miracidia within the eggs before the feces are diluted by water.

b. The parasite within the intermediate host. This becomes the problem of the destruction of the molluscan host. Since the snail is a macroscopic animal and lives mainly in shallow water or on the adjacent shore, it is available for destruction when once the exact location of the snail is known. The practicability of attempting the destruction of the snail depends mainly on the extent of its distribution,

and upon the discovery of a simple method for its extinction. Unless a natural enemy of the snail can be found, this method can be applied only by public health workers. The cooperation of the native population in China cannot be expected in such a project at the present time.

c. The liberated cercariae can be prevented from infecting the mammalian host by three methods:

(*a*) By killing the cercariae in the water by some chemical, such as chloride of lime.

(*b*) By avoiding the use of water inhabited by cercariae until the cercariae have died. This would require storage for at least forty-eight hours.

(*c*) By protecting the skin of the mammalian host from contact with the cercariae. In the case of man this would mean educating him, first, to avoid immersion in canals and other similar bodies of water in regions known or believed to be infected, and, second, to cover effectively his limbs when working in the rice fields. The elimination of other mammalian hosts from endemic regions may also be considered from this point of view.

Prophylactic work in Japan.

In proving that the skin was the portal of entry of the parasite, Fujinami and Nakamura (1909) demonstrated for the first time a means of preventing the infection. In their experiments, calves, which were known to be susceptible to the infection, were provided with water-proof cloth leggings which prevented their becoming infected when immersed in "infected water." It has been more recently determined that a double layer of cotton cloth with a mesh of not over 100 micra is sufficient covering to prevent infection. This knowledge has not been put to any great practical use, however, for it involves the purchase of clothing by farmers, to be worn contrary to their custom and comfort.

The next step taken in Japan was an attempt to prevent infection by killing the infecting agent (i.e., the molluscan intermediate host). This was begun by Fujinami and Nakamura (1912) before the cercaria of the worm was known. Miyagawa (1913) and others followed with similar experiments, and it soon became evident that the infection could be prevented by a number of chemical substances which would not injure, but would rather increase the fertility of the ground. Unslaked lime (CaO), and calcium cyanamid (CaN.CN), both of definite

fertilizing value, were found to produce excellent results. Beside these, calcium phosphate ($Ca_3 (PO_4)_2$) and ammonium sulphate ($(NH_4)_2SO_4$), which also have fertilizing value, were found to have considerable, though less, prophylactic value. Chlorinated lime (CaClOCl) and copper sulphate ($CuSO_4$), though efficacious, were detrimental to the crops.

With the discovery of the intermediate host and the coincident recognition of the cercaria, it was demonstrated that these chemicals acted both on the parasite and on its intermediate host, so that their action in the prevention of the disease was two-fold and of apparent practical value. Fujinami and his co-workers followed up their former observations by practical application in the endemic region of Katayama (Fujinami and Sueyasu, 1919). They found that in a concentration of 0.1 per cent, calcium oxide (CaO) killed all the snails in five days, while calcium cyanamid in a similar concentration produced the same results within about three days. Calcium oxide, being cheaper, is now used extensively in endemic areas in Japan in destroying the intermediate host. In irrigation ditches it is employed at an estimated concentration of one per cent. It is spread thickly on the banks and in the slowly moving water. In the rice fields a 0.1 per cent. solution is used, since the stronger solution tends to injure the crops, especially in places where there is considerable alkali in the soil itself.

Fujinami and Sueyasu (1919) also investigated the possibility of killing the snail by heat. At first hot water was used, since it was known that the snail instantly died in water at a temperature of 60° C. It was found, however, that even boiling water was quickly cooled to below the lethal point when sprinkled on the ground, and that the snails which clung to the roots of the grass were not killed. Live steam was next applied, and was found to be more efficacious. In practise it is pumped from a boiler through a hose, and expelled beneath a piece of heavy canvas spread upon the ridges of earth bordering rice fields. When applied to a single area for a few moments, ninety per cent. of the snails in the area are killed. This has been tried out extensively in the Katayama area, but has been found to be less valuable than the lime method. It is at most expensive and cumbersome in operation.

Sea water was found to be very effective in killing the intermediate host. The best practical application of this agent was seen when a tidal wave inundated a portion of the endemic area in Shizuoka Province. We tested in the laboratory the action of sea-water on Japanese Katayama snails and found that a strength of equal parts of sea water and tapwater would kill the snails in twenty-four hours.

This method of destroying the intermediate host might quickly rid a large area of the snail in a very short time, if applied during a dry season of the year, in a region located close to the ocean, as some of the Japanese endemic areas are. The initial cost of such a project would probably be prohibitive, and it would require the cooperation of the population to an extent not easily secured.

The control of the disease by killing the eggs in the human feces has also been studied carefully in Japan. Miyagawa (1916) studied the effects on the eggs of various physical and chemical conditions. He found that a temperature of 25° to 30° C. was optimum for the hatching of the miracidia, that 37° C. or over was quite unfavorable for hatching*, that direct sunlight (?) was detrimental to hatching, that oxygen was necessary for the development of the miracidia, that in urine or in a urine-feces mixture the miracidia within the eggs failed to hatch and died within 16 days, and that the chemicals which killed the intermediate host and cercariae also killed the miracidia.

Of these facts the lethal effect of the urine and feces on the egg is the most readily applicable, and has been used by the Japanese as far as possible. The storage of all fecal material for three weeks before using it on the rice fields has been urged upon the people of endemic areas. The success of such a measure demands efficient supervision by public health authorities. It must be supplemented by the prevention of promiscuous defecation by children or persons suffering from diarrhea and dysentery.

Finally the elimination of mammalian hosts other than man from the endemic areas has been attempted by the Japanese. Oxen, dogs and cats were recognized from the first as the most important reservoir hosts, and more recently the field rat (Sueyasu, 1920) has been charged with playing an important rôle in perpetuating the disease. Fujinami and Nakamura (1913) demonstrated that the horse, though susceptible to the infection, rarely passed eggs in the feces, and seemed to acquire immunity against the disease after the first infection. Oxen are therefore being replaced by horses in endemic areas, and the possession of cats and dogs is discouraged. The field rat is a much more difficult factor with which to deal.

That considerable headway has been made in eradicating the disease from Japan is evident from recent reports. Nakamoto, who is in charge of this work in the Katayama area, writes in a personal com-

*Our results are not in accordance with Miyagawa's, since we found the range for hatching of the miracidia to be much wider. Possibly we were working with a hardier batch of eggs (See Section II, A).

munication as follows: "For several years lime (CaO) disinfection has been practiced in our (Katayama) district. Prohibition of oxen will be declared shortly by the authorities. The dredging of the river has long been discussed and is now at hand. We have already accomplished partial eradication of the snail. The small east area is now cleared of both the snail and the disease. In the large west area the infection has been much reduced."

The problem of bilharziosis in Egypt.

In the countries where bilharziosis exists conditions on the various aspects of the problem differ to a greater or lesser degree from those obtaining in schistosomiasis japonica. In Egypt and the Anglo-Egyptian Sudan both schistosomiasis haematobia and schistosomiasis mansoni exist, although the former is much more prevalent and, by reason of the eggs being evacuated in the urine, is much more readily diagnosed. The facility with which eggs may be found in vesical bilharziosis may constitute a reason why fewer cases of *Schistosoma mansoni* infection are diagnosed. Nevertheless, the conditions under which both diseases are spread and perpetuated are essentially the same. The arable land lies in the immediate vicinity of the Nile or in tracts of ground irrigated from the Nile. The inhabitants are Mohammedans and are enjoined by holy writ to cleanse with water the parts of the body polluted by defecation or urination. Ablutions are particularly required before the hours of prayer. In order that time and opportunity may be conveniently joined, the evacuation of body excreta is ordinarily made near or into a canal or irrigation ditch. Whether it be vesical or rectal bilharziosis, the medium in which the egg has been evacuated becomes diluted by water and the miracidium hatches. Eggs of *Schistosoma haematobium* will not hatch in undiluted urine, although they will remain viable in the medium for some time, but they hatch almost immediately when transferred to water. Both genera of molluscs, Isadora and Planorbis, involved in these two infections in Egypt are found close together in essentiallly the same place, where they were when the Nile irrigation projects were first initiated. They are non-operculate snails and are consequently killed by prolonged draining of the canals. But they apparently reestablish themselves with ease. A new irrigation project in the Nile Valley means a new center of bilharziosis.

Through the courtesy of Doctor M. Khalil, Helminthologist of the Public Health Laboratories at Cairo, one of us (E. C. F.) has had the opportunity of observing the conditions responsible for the propa-

gation of the disease in the heavily infected regions at Qaliub and El Marg, a few miles north of Cairo, and has witnessed the out-patient treatment of cases in the Government hospital at Qaliub.

Epidemiological and biological phases of bilharziosis.

Apparently the first investigator in an endemic area of bilharziosis, who advocated a theory as to the mechanism of infection with the organism, was Allen (1888), who, working in Natal, South Africa, formulated the belief that "nearly all the youths bathing in the Umsindusi and Dorpspruit are infected, while the girls, who do not bathe, remain free of the disease." The skin route of infection was likewise maintained by Looss, although he was forced to the conclusion that the schistosome was a monogenetic trematode and that the miracidium, when once hatched from the egg, directly invaded man without the intercalation of the sporocyst generations. It remained for Leiper (1915–1918), after visiting the Orient and observing and confirming the work of Japanese investigators on the life history of *Schistosoma japonicum* (Leiper and Atkinson, 1915) to study the problem in Egypt and experimentally to prove, (1) that the Egyptian schistosome infections were of two kinds, produced by two specifically different schistosomes, of which *Schistosoma haematobium* was the causal organism in vesical bilharziosis and *S. mansoni* the responsible one in rectal bilharziosis; and (2) that both species underwent an alternation of generations, with molluscs as intermediate hosts. Leiper (l.c.) further studied the problem with reference to its prophylactic aspects, and found a causal connection between the irrigation projects in the region of El Marg and along the freshwater canal, and the propagation of the disease. After discovering that the snails would not survive drought, he concluded that for the native districts care should be taken to align the irrigation canals, so that, at the periodical stoppages of water through the central governmental control system of the Nile River, no residual pools or ditches should exist in which the molluscs could "tide over" until the next periodical supply of water was let into the canal. This was believed to constitute a benefit to the principal summer crop, cotton, but was recognized as a possible detriment to the rice fields. Ammonium sulphate was advocated as a chemical which could be used in treating pools to destroy the surviving molluscs. For bathing, drinking and household purposes Leiper proposed that unfiltered water either be stored for a period of forty-eight hours (care being taken that none of the molluscan hosts were present in the storage tanks), or treated with chlorinated lime or other chemical, lethal for the cercariae.

With the introduction of antimony tartrate therapy for bilharziosis by Christopherson in 1917 (1918), treatment of infected individuals was carried on in large units. Only those critically ill were treated on the ward, the great majority of cases being cared for in out-patient clinics. In this way thousands of cases have been cured or helped each year. A preponderance of such cases suffer from schistosomiasis haematobia. Diagnosis is relatively simple, since hematuria or the presence of albumin in the urine is usually an accompaniment of vesical bilharziosis, and since eggs are relatively easy to find in the urine in most of these cases without centrifugalization. On the other hand, diagnosis in rectal bilharziosis is more difficult of microscopic confirmation, since the ova are distributed throughout the stool and do not seem to be concentrated in flecks of bloody mucus, as one ordinarily finds them in schistosomiasis japonica. In neither vesical nor rectal bilharziosis does the patient seem to suffer such a drain on the system as in schistosomiasis japonica, where portal stasis and hepatic cirrhosis are more pronounced. Neither is the incidence of morbidity as high nor the mortality as great as in schistosomiasis japonica.

In view of these facts it is relevant to the problem in hand to inquire what progress has been made in combating the disease in Egypt during the interval since the proof of the life history of the Egyptian schistosomes has been a matter of common knowledge, and since satisfactory methods for destroying the molluscs have been understood.

1. *The adult worm and the egg in the mammalian host.* The hospital in the village of Qaliub, twelve miles north of Cairo on the railroad to Port Said, may be taken as typical of the several government organizations devoted to medical welfare in Lower Egypt. In addition to the usual medical services this hospital has a temporary unit engaged in bilharzia-therapy. Two well qualified native doctors are assigned to this work. One makes the diagnosis of cases, while the other administers treatment. The infection consists almost entirely of the vesical type and is found mostly among males from ten to fifty years old, who are usually field laborers. Among those who operate the spiral water lift (Fig. 1) the incidence of infection is particularly high. Heavy infections cause albuminuria and hematuria with accompanying pain, but many, with light infections, have no pronounced clinical symptoms. The eggs are ordinarily found without centrifugalization by allowing the urine to stand and examining the sediment. Treatment of all cases diagnosed as positive is given in the out-patient clinic. It consists of the intravenous injection of sodium antimony tartrate,

1 to 2 c.c. of a 6 per cent. solution being administered every other day, until twelve doses have been given. One hundred and fifty such treatments are cared for each day, six days a week, making a total of more than four thousand patients treated for the infection in this one clinic a year. The most significant fact aside from the specificity of the drug for the disease is the cheerful cooperation of the patients. In the large Kasr el Aini Hospital in Cairo, plans are under way for an anthelminthic clinic to care for twelve hundred cases per day, most of whom will consist of bilharzia patients.

No mammals in Egypt have been found to constitute a serious reservoir of infection with *Schistosoma haematobium* or *S. mansoni*, so there has been no need for prophylactic work in that direction.

2. *The extra-mammalian forms of the parasite.* (*a*) *Feces and urine disposal.* El Marg, the village where Professor Leiper worked out the basis for prophylactic work on bilharziosis in 1915, may be considered as typical of the conditions that prevailed in the Lower Nile Valley when we visited the endemic area in the summer of 1923. As in the past, the water supply in the canals was intermittent, being off for five days and then on for a period. One small canal wandered through the village (Fig. 2) serving both as a rendezvous for the washerwomen of the place and as the village sewer, including sewage from both the homes and the village mosque (Fig. 3). As in the past, before the dangers of the infection were understood, the villagers urinate and defecate into or near the stream so that the required ablutions may be easily performed. The same conditions prevail in the farming plots in the neighborhood, although the smaller amount of excreta no doubt makes the chance of infection somewhat less. No disinfection of the excreta has been carried out, although we are informed that an attempt is being made by public health officers to prevail upon the priests to provide other means for ablutions.

(*b*) *The molluscan host.* There has been no definite program to destroy the molluscan hosts in the infected areas. Although the snails and eggs (Khalil, 1922) are mostly killed in the main canals and ditches during the period when the water is shut off, the residual pools have been adequate to keep the ditches stocked with snails. When we visited the village, the water had just been turned into the canals, and few snails were to be found in the canal within the village, but *Isadora* (*Bullinus*) *truncata* was collected in considerable numbers just north of the village (Fig. 4).

(*c*) *The liberated cercariae.* In the villages the women still expose themselves by washing their clothes in "infected water." In the

country, where the water is conveyed from the canals into the field-ditches by means of a hand-operated spiral lift, the operator sits on the upper side of the machine (Fig. 1), with his legs in the water, exposed for hours at a time to the entire supply of "infected water," as it passes by him. "Itching" of the limbs occurs during this period where the water surface comes in contact with them, but later, on leaving the water, the entire surface of the limbs below the water level constitutes a potential area of infection as the water film begins to dry.

Discussion.

Whether the present policy of relying entirely on therapeutic prophylaxis will ever succeed in reducing the infection in Egypt depends largely on the percentage of the whole population treated. Perhaps with a more general treatment of cases in endemic areas a point will be reached where so few viable eggs are available for development that the infection will be gradually wiped out.

Features of the prophylaxis problem peculiar to China.

In China there are certain conditions which make the prophylaxis of schistosomiasis japonica quite different from what it is in Japan and in many ways unrelated to the preventive aspects of bilharziosis in Egypt. These conditions may be briefly stated as follows.

1. The extent of distribution of the disease and of the intermediate host. The distribution of the disease has already been outlined as far as our present knowledge goes (see section V). Japan's endemic area is negligible in extent when compared with the vast territory from which the disease is reported in China. The Katayama area in Japan, for instance, contains only about ten square miles of rice land, and Nakamoto found that, within this area, the intermediate host was present over an area of only about two and a half square miles. In addition to the Katayama area there are only four other endemic regions in Japan, none of which is very much larger than the Katayama area. In comparing this with the endemic regions of China one is immediately impressed with the greater extent of the Chinese territory. The Shaokan-Tsaoshih area in Hupeh Province, for instance, which is the smallest endemic region of the Yangtze basin, has an area of about 600 square miles, when estimated on the basis of case reports at the Tsaoshih hospital. Since this is mainly a rice growing region the intermediate host may extend over a much greater territory. The Soochow-Kashing area, in the lower Yangtze basin, covers an area of approximately 10,000 square miles, of which at least one half is com-

posed of rice fields and canals which are irregularly inhabited by the intermediate host (*Oncomelania hupensis*). It is impossible to estimate with any degree of accuracy the total extent of distribution of the disease in China, but it is probable that the rice-growing country in which both the disease and the intermediate host are present covers at least 25,000 square miles. This estimate may be too low, for it comprises only about one third of the total rice-growing area of China, as estimated by King (1911: 272). From this point of view alone, it is evident that any effective prophylactic work must be of a type in which the inhabitants of the region will cooperate. It cannot be left entirely to public health workers.

The intensity of infection in any given area varies greatly, both in the number of people infected and in the severity of the infection. In general it may be stated that the larger the number of infected persons in a given village, the more intense is the infection in those individuals. This is because of the vicious cycle produced by the continuous exposure and the continuous evacuation of eggs. The small amount of traveling done by the farmers tends to intensify the infection in infected villages and to prevent its spread to others. For this reason it is common to find villages in heavily infected regions where no clinical cases exist.* The increase of travel which is sure to come with the improvement in communications, particularly by railroads and motor boats, will tend to spread the disease more diffusely throughout the area inhabited by the intermediate host.

It is impossible to state at the present time with any degree of accuracy how great a total physical disability and economic loss are produced in China by schistosomiasis. We do know that, in children, the disease often stunts growth and delays adolescence for several years, and that many deaths are caused by it in late youth and in early and middle adult life. Our meager observations have demonstrated that, in some villages, 50 to 75 per cent. of the inhabitants are infected, and we believe that, wherever this is true, about 20 per cent. of those infected die as a direct result of this infection.

In comparison with other helminth infections, schistosomiasis is considered by many of the physicians in the endemic regions in China to be the most important in creating physical disability, death and economic loss. Hookworm disease is prevalent throughout the schistosomiasis regions, but the *clinical results of hookworm infection in China are usually slight, as compared with those of schistosomiasis.*

* Hard-packed clayey soil, along the banks of canals, in infected regions, precludes the possibility of the snail's development (see Section IV) and in this way prevents certain localities from becoming endemic for the disease.

2. *Governmental control.* This is one of the most important requirements for successful public health work. Without it there is no police power to enforce the cooperation of ignorant people in general health measures. Japan has been fortunate in having this cooperation in combating schistosomiasis. In China, however, civil government is limited, for the most part, to tax collection and to an attempt to preserve order. With rare exceptions, neither the provincial nor the local authorities have any interest in the welfare of the inhabitants. Furthermore, the Chinese are very jealous of personal liberty, and matters which concern their personal habits or the pursuit of their occupation are considered outside the province of governmental activity. They view the activities of any person, not a native of the immediate community, with suspicion and distrust.

3. *The ignorance and superstition* among the peasant population of China is extreme. Schools are found only in towns and cities, and most of these are of a very low grade, teaching only the rudiments of the Chinese language and moral code. Mission schools and hospitals are so few that their influence in public health measures is only felt in the immediate field which they serve. The education of the farmers to any realization of the necessity of protective measures against such an infection will require generations of active effort on a large scale. Furthermore, many educated Chinese believe that the Chinese people are not subject to the same laws of personal hygiene which apply to Occidentals, but are peculiarly immune to many infections which menace other peoples.

The relation of rice farming to schistosomiasis.

Since schistosomiasis in China is limited almost entirely to rice-growing territory and is most closely associated with this occupation, it is profitable to review briefly the methods used by the farmers.

Throughout the entire Yangtze Valley and the regions adjacent to the three large lakes lying to the south of the River, one or two crops of rice are obtained each year. From Foochow southward, however, three crops are often obtained. It will be sufficient to give the program followed in the Yangtze Valley. The rice is planted from seed by sowing into small nursery beds close to the habitations and water supply. These are planted in April or May. The ground is prepared, from two to four weeks in advance, by the application of human feces and other fertilizer, and by plowing, harrowing and bedding with plant ashes. The rice seed is then sown, and the field is flooded with water. After this the nursery bed is alternately drained and flooded

until the plants are well started. Then a layer of water one or two inches deep is left on the field. At the end of four weeks the young seed plants are about eight inches tall and are ready for transplanting (Fig. 5). Meanwhile the permanent rice fields have been prepared, and in May or June the transplanting is done. The women are usually responsible for pulling up and stacking the seedling plants, but the whole family often joins in the work. They squat barefooted in the flooded nursery beds for hours at a time, stacking the little plants in bundles of convenient size. These are then removed to the permanent field, often by the children. The men do most of the transplanting. The permanent field is flooded to a depth of two or three inches, and the men wade barefooted through the water, setting out the plants at proper intervals (Fig. 5). Until the plants are well established, considerable water is kept on the fields. Later, when the plants are two feet high or more, the soil is sometimes allowed to dry until it cracks open. Water should be always at hand, however, to flood the fields at the proper time. They are hoed and fertilized at intervals during the summer, requiring the farmers to go occasionally into the water, always in bare feet. Only at the harvest time, and sometimes not even then, is the ground permanently dry.

In some parts of the Yangtze Valley the first rice crop is harvested early in August. This gives sufficient time for a second crop. The nursery beds are replanted in July to prepare for this, so that no time is lost in starting the new crop. This doubles the exposure of the farmers and their families to the water of the nursery beds and increases the necessity for the permanent rice fields to be immersed and to be visited by the farmers. Furthermore, the opportunity for snails to become infected with *Schistosoma japonicum* has been increased greatly through the warm season, by the fertilizing of the soil, so that the nursery beds are much more dangerous at the second transplanting. The water from canals or ponds is also more likely to contain cercariae at this time than it is earlier in the summer.

After the final rice crop is gathered, more fertilizing is necessary by the spreading of human excreta and vegetable materials, and throughout nearly the whole Yangtze Valley a winter crop of wheat is sown, and is reaped in the spring shortly before the transplanting of the rice. In the wheat crop season the fields are dry, so that this period is not important in relation to schistosomiasis.

The points of contact of the rice farmer with the infective (cercarial) stage of *Schistosoma japonicum* are made by three necessary features of the farming process, namely:

1. Fertilizing of the fields with human feces.
2. Flooding of the fields.
3. Wading in flooded fields.

These will now be discussed in more detail.

1. The custom throughout the rice-growing country is to preserve the human excreta in huge earthenware containers, called "kangs" (Fig. 9), which are at times set deeply into the earth, so that they may be more conveniently used. In some regions a rectangular pit, walled with stone, is used as a village cesspit (Fig. 10). The women use commodes inside the houses, which are emptied daily by the youngest daughter-in-law in the family into the "kangs" and washed out in a nearby canal. The "kangs" are emptied whenever it is advantageous for the fields to recieve the fertilizer, usually about once in four weeks. *Both fresh and ripened excreta are present in each "kang" at the time it is emptied.* The material is removed in huge wicker ladles or gourds and poured into buckets, from which it is spread upon the fields. Fresh feces are considered better than feces which have ripened, and are used particularly on the nursery beds. The "kangs" are probably never washed out, but the stone-walled cesspits are cleaned at intervals and the washings emptied in the canals. The buckets and ladles are also washed in the canals periodically.

2. The flooding of the fields is accomplished almost entirely by mechanical means. The tread wheel, revolved by human foot power (Figs. 7, 8), and the horizontal cog wheel (Fig. 6), revolved by oxen or water buffalo, are used entirely in the flat country. Sweeps or vertical wheels are necessary in terraced hill country. A box trough leading from the canal, lake or pond up to the rice field carries the water and whatever is in it into an irrigation ditch which leads out between the fields. In the region about Kashing, Chekiang Province, in the month of June, we found these ditches inhabited by great numbers of *Oncomelania hupensis.* The great variation in the size of these snails indicated that they were probably reproducing there, although some must have been carried up directly from the canals. In either case the water passing by the tread-wheel coolies is undoubtedly "infected water" and a constant source of infection to these individuals. As we have already stated, the nursery beds are usually the fields nearest to the canals. We also found the snails in enormous numbers in some of these beds at the time when the rice plants were just ready for transplantation. Fields farther away from the canals did not contain the snails, even though flooded and ready to receive the young plants. Cercariae which had escaped from snails in the canal

could, of course, be carried in the irrigating water into fields at a distance from the canals, but would be relatively few in number, and some would be injured by the churning of the water. In endemic regions which we have not yet investigated, it may be found that, as in Japan, the permanent rice fields also are inhabited by many snails. As far as our observations go, however, *the nursery beds are by far the most dangerous foci of infection.*

3. The entry of the farmers directly into the flooded rice fields is an absolute necessity. Furthermore, both comfort and economy prescribe bare arms and legs for the work to be performed. The cloth or straw shoe usually worn by these people would be little protection against infection, and ordinary trousers or socks would be no better. All these would soon be ruined by the water and mud. Gloves of rubber, leather or heavy cloth would be cumbersome and expensive and would decrease the speed of the work.

The relation of other occupations to schistosomiasis.

Aside from the rice farmers, boatmen are the principal sufferers from schistosomiasis in China. In the endemic regions transportation is mainly by water. Within many cities canals are the main thoroughfares, and in the flat rice country, outside the cities, canals are practically the only continuous routes of travel. For transportation of freight over long distances the sailing "junk" is employed, but the large majority of the boats are the small "sam-pans" (Fig. 11) and the larger house-boats (Fig. 12), both of which are flat-bottomed boats, propelled by a single stern oar. In the cities thousands of these swarm about the canals, and in the country districts nearly every family possesses at least one. Those, whose occupation is mainly on the water, live on their boats, and such a habitation may be changed only once or twice in a life-time. The men and children defecate from these boats directly into the water, the women use commodes which are later emptied into the canals and washed out there. The children of these people swim in the canals, the men wade into the water to clean or repair the boats, and to tie them up at banks and landings, the women wash their rice and household utensils in the canal, and the unboiled canal water is used on the boats for all "necessary" purposes, including the cleansing of the teeth. The entire life of these people is therefore in most intimate contact with the water on which they dwell.

Although the boatment find most of their employment in and about cities, where conditions are not so favorable for the existence of

the intermediate host of *Schistosoma japonicum*, their work frequently carries them into the country districts where they are more exposed to infection. They are also an important factor in the dissemination of the disease, because, when once infected, they are of potential danger to any uninfected village to which they may go (subject of course to the presence of the molluscan host in that particular neighborhood). Boatmen with schistosomiasis have been encountered who have traveled as far as fifteen hundred miles along the Yangtze River.

Within the cities, in most of the rice-growing territory, the system of feces disposal also contributes to the spread of schistosomiasis. Here feces are deposited either in public "kangs," or in commodes or "kangs" within the private homes. The material from these receptacles is collected by boatmen in "sam-pans," and the commodes are washed in the canals. This can be most commonly observed as one passes along the canals of a large city at daybreak, when the commodes and vegetables are being cleaned in the canals. In the "sam-pans," the night-soil is carried into the farm country, where it is sold to the farmers and stored in "kangs" or pits until needed. We found the intermediate host, *Oncomelania hupensis*, on the shores of canals within the city of Soochow, and it undoubtedly exists in other cities. Furthermore, cases of schistosomiasis are frequently found in people who live in large cities. All the conditions are present, therefore, for the propagation of the disease among the urban population of endemic regions. However, the relatively slight contact of the city people with canal water makes the problem here a much less serious one than it is among boatmen and farmers.

Foreigners in China who become infected with *Schistosoma japonicum* do not contribute seriously to the general problem of prophylaxis; but, because of their prominence among the cases seen by foreign physicians, they should be mentioned as a part of the problem. The cases in foreigners have been in three groups, namely: sportsmen who wade through the ponds and rice fields, while snipe-shooting; children who fish and bathe in ponds, lakes, and canals; and sailors on foreign war vessels along the Yangtze River and its tributaries who are compelled to enter infected water to clean their boats, or who bathe in such water. Education of all foreigners in endemic areas and of the naval authorities of nations having war vessels in these waters, as to the proper precautions to be taken, is all that is needed and should be a relatively simple matter. It is difficult to understand why the naval medical authorities of the nations concerned have not long ago issued orders which would prevent their sailors from acquiring this disease.

Yet cases still occur among officers and sailors who have not been sufficiently warned or instructed how to prevent infection (see Section VII; also Sanders and Priston 1921). Proper precaution heretofore may have been neglected by uncertainty as to the type of water containing the infection, but it is now evident that deep lake or river water in regions where gunboats are anchored, is the least likely to harbor the infection.

Methods to be used in China.

It is evident that the problem of eradicating schistosomiasis from China is an extremely complex one. It is not merely a public health problem; for within its scope are also included problems of economic and political life and general education. If this disease were present in a scientifically enlightened country with an efficient government, it would be feasible to eradicate it from even such a vast area within a few years. In China the conclusion of the task is much more distant. The immediate question which faces those who are interested in the problem is, *what measures will be most effective with the agencies which are at present available.*

Emphasis should be placed upon measures in which the habits of the people may be used as an asset. Under the prevailing conditions we would recommend the following procedures in order of their importance:

1. *Control of contaminated feces.* This can be accomplished by educational measures among the rice farmers. Four sanitary measures are necessary to secure this control. These are:

(*a*) *Adequate storage of feces.* The addition of an extra "kang" to the present equipment of each place for fecal deposition would permit the storage of feces in one "kang" for a period of three weeks or more after it is last used. Experiments have shown that this is sufficient time for the killing of all schistosome eggs in a feces-urine mixture, provided it has not been diluted with water. Here is an additional difficulty, since the excreta are commonly diluted with several parts of water. A cover fastened over such a "kang" would prevent its further use, until the death of the eggs had been effected. The application to these "kangs" of some chemical which would kill the eggs and miracidia, would obviate the necessity of storage for so long a time. If such a chemical had fertilizing properties of its own it would make an additional appeal to the farmers. Experiments along this line should be conducted, keeping also in mind the possibility of killing other infective organisms. Hookworm and other

helminth eggs are more difficult to destroy than those of the schistosomes, but fly larvae, amebae and other protozoa, and pathogenic bacteria are more susceptible to destruction by chemicals. The anti-fly work now being done by Dr. C. W. Woodworth in Nanking, China,* by the application of sodium cyanide to the "kangs" where fly larvae are present, may offer an opportunity for cooperative work along this line. Even a sufficient commingling of ricestraw ash might be effective.

(*b*) *The avoidance of promiscuous defecation.* This may be nearly as great a source of infection of the snails, as the use of insufficiently stored feces. On the farms, children and persons suffering from diarrhea, as well as dogs, are the chief offenders. Where fecal deposition is necessary outside the usual "kangs," the farm people should be taught to deposit it in a dry place, away from canals and to cover it with lime or ash to disinfect it and to avoid its being washed by rain into a nearby body of water. Among the boatmen the problem is much more difficult. Beside instructing them in the dangers of promiscuous defecation, it will be necessary to establish convenient places for their use and to offer some additional inducement like the purchase of daily accumulations of excreta. Such public conveniences are actually in use in parts of Chekiang Province, and are made as attractive as possible to induce the traveller to make use of them. It is a purely money-making proposition, since the night-soil can then be sold for fertilizer at a good price. This will require extensive activity by public health organizations.

(*c*) *Commodes used within the houses* should be sterilized before they are washed in the canals. This will probably be a difficult procedure to institute. It will require the possession of an antiseptic or the scalding of these containers, either of which is at present highly impracticable. Lime would probably not be effective for the rapid destruction of the larvae. Perhaps nothing would be reliable in the hands of the irresponsible person who has this menial work to do. To have the water which is used for washing out these "kangs" poured out on the dry ground rather than into the canal, may be the most efficient and simplest precaution to be advocated. Buckets and dippers, used in transporting the fertilizer, should also be sterilized or, when possible, dried for several days in the sun. On the whole this part of the program would seem to be the most difficult to put into operation.

(*d*) *The elimination of reservoir hosts.* It is not yet known to what

* Private report to International Health Board by Dr. J. B. Grant.

extent domestic animals and rats contribute to the perpetuation of the disease in China. Water buffalo probably are not a factor; oxen may be, as they are in Japan, but are not so common as in Japan. It is known that foreign hunting dogs rapidly become infected in the endemic areas, but there are no reliable data on the Chinese dogs, who are proverbially averse to going into the water. Infection among cats should also be investigated. Rats are present in towns in endemic areas, and often inhabit the stone walls bordering on the canals. Field rats are not known to exist in any great number in the regions which we have investigated. In general we have the impression that in those endemic areas in China which we have investigated, the reservoir hosts of this parasite are considerably less important than they are in Japan.

2. *Avoidance of contact with infected water.* This is also a purely educational measure.

(*a*) *The small terminal canal and the irrigation ditch* are the most potent sources of infection, and there is practically no necessity for the farmers to enter this water. However, it is the water usually nearest his "doorstep" and most likely to be waded through in tying up the boats. These places are probably where the children acquire most of their infection.

(*b*) *The rice nursery beds,* being nearest to the canals, and being also the fields to which fresh excreta are most often applied, are the most dangerous of the rice fields. The protection of the feet and hands, while pulling up the young rice plants, would be necessary for a few days only, and would remove most of the danger from that source. *Children should be kept out of these fields entirely. The substitution of some other form of fertilizer on these small beds would entail little additional expense and would, at the same time, kill the intermediate host and prevent the infection from entering any snails which remained alive.*

(*c*) *The permanent rice fields* are the least dangerous, as far as our observations go, and the adoption of hand and foot coverings for the farmers when they work in those fields would be a most difficult preventive measure to put into practice. That may be postponed, however, until the other educational measures are farther advanced. A heavy oil or grease spread thickly on the lower legs and arms may prove to be of some value, and would be more practical than the wearing of heavy gloves or stockings.

(*d*) *The protection of foreigners from infection* can be secured easily by proper educational propaganda. Throughout the Yangtze Valley, ponds, small lakes and canals are dangerous bodies of water from

March through November. Only in the centers of large lakes and in swiftly running streams should out-door bathing be permitted. Hunters should be taught to protect themselves during the dangerous months by wearing high rubber boots or two or three complete layers of closely woven cloth garments. Naval orders should be issued which would prevent the infection of sailors while performing duty and which would instruct them how to avoid infection when off duty. There is now no need for such infection among the sailors of a properly disciplined gunboat.

3. *Specific treatment of the disease.* It has been demonstrated that sodium or potassium antimony tartrate, administered intravenously in an intensive course of treatment, will cure schistosomiasis. Emetine also is possibly curative in large doses, but needs more trial. Extensive out-patient treatment, such as is successfully carried on in Egypt by qualified hospitals throughout the endemic regions, would do much to lessen the mortality and economic loss from the disease and would lessen the number of "carriers." *Successful treatment of the disease would also be a potent factor in the education of the people, by gaining their confidence in the advice given, and cooperation in the carrying out of preventive measures.* This is a most important adjunct to direct prophylactic work and should occupy a large place in the program of all hospitals in endemic areas. No doubt, if this therapeutic prophylaxis were systematically carried out, it would soon assume a very important place in the preventive program.

4. *Extermination of the intermediate host.* This is placed last in importance, because of the tremendous extent of the snail's distribution, and because it is not a measure in which the cooperation of the inhabitants can be secured. It will be discussed here very briefly as the methods available have already been described (see Section IV). Even if one were dealing with schistosomiasis haematobia in China, with non-operculate molluscs as intermediate hosts, the problem of eradication would be an infinitely more complex and perplexing one than it is in Egypt. Irrigation in China is not under government control, but under individual activity of each and every one of the many millions of farmers owning or renting a plot of farming land in the rice-growing areas. Cooperation could be secured only as each farmer in question had been converted to the project of destruction of the molluscs. Even then the proposal of Chandler (1920) to use dilutions of copper sulphate to exterminate the snail would be impracticable, since, as Khalil and Lee (1923) have shown, the amount of dilution which is lethal to the snail in aerated water, is least efficacious

in stream water rich in organic matter. Furthermore, we are not convinced that this dilution is not harmful to the young rice plants. However, we have shown conclusively that the intermediate hosts of *Schistosoma japonicum* are very different bionomically from the non-operculate snails involved in Egyptian bilharziosis. If they were purely aquatic organisms, the fact that they are operculate molluscs complicates the problem. But they are essentially amphibious in habits, and at times almost purely terrestrial. If they could be reached by chemicals sprinkled along the banks or in the fields, such chemicals would have to be non-toxic to the vegetation. After all, when the snail escapes a trained field biologist, as it has at least twice in China, when such workers were searching for molluscs in the very region where infected Oncomelanias were later found, it is rather too much to expect that in each center known to be endemic for schistosomiasis japonica an accurate census map of the location of Oncomelanias be secured. Search should be made, however, for some more efficient method of exterminating this snail. The introduction of a natural enemy, as for example, a soil nematode or beetle larva, would be the most efficient means of reducing the snail population, and investigation of the intermediate host is the surest method of breaking the life cycle of the parasite.

Immediate steps to be taken in China.

Many agencies now available may contribute in the near future to the beginning of prophylactic work against schistosomiasis in China. The following activities are urged as being immediately practicable:

1. *Further study of the disease.* Particularly is it important to know the exact distribution of the disease in China, and to know whether it is still spreading. Careful routine microscopic examination of the feces of all patients applying for treatment to foreign and Chinese hospitals, in rice growing regions, would undoubtedly reveal the presence of schistosomiasis in many places now believed to be free from it. The reporting of these results would give us a better knowledge of the extent of our problem, and the accumulation of such data for a few years might reveal the constant spreading of the disease.

2. *Further research for the intermediate host.* So far we know the distribution of *Oncomelania hupensis* and *Katayama nosophora* in China only through our own observations in Kiangsu, Chekiang and Kwangtung Provinces, and through the collections of Heude (1890), who knew nothing of *Schistosoma japonicum*. Search should be made for the intermediate host in all parts of the rice-growing regions of

China by physicians, biologists and others who may be interested in the problem. We have already indicated (Meleney and Faust, 1923) how the search should be made. It is evident that in certain types of country in China, especially in regions geographically similar to Japan, *Katayama* acts as the intermediate host. It may be, also, that a third or even a fourth species of snail may be found to act as the host in other regions of China, not yet investigated.

3. *A study of the biology of the intermediate host.* This might reveal some period at which the snail could be attacked most successfully by a natural enemy or by methods not now considered feasible.

4. *Intensive study of a small area* to determine what factors are most important in spreading the disease, particularly among rice farmers and boatmen. This would include a detailed study of the habits of the people, their methods of farming, the viability of eggs under various conditions, and the migrations of the intermediate host under changing climatic conditions.

5. *Experimentation with methods of prophylaxis* in a small area. In this work the possibility should be kept in mind of developing methods which may also be successful against other parasites, such as hookworm, Fasciolopsis, or against vectors of disease such as flies.

6. *Demonstration of specific treatment of schistosomiasis* in a small number of well equipped hospitals. The possibility of using intensive methods of treatment with antimony, the relative efficacy of this drug and of emetine in early and late cases, and the feasibility of establishing out-patient clinics for this specific treatment should be kept in mind in such a demonstration.

7. *Educational propaganda* through hospitals, schools and all other available agencies, to start the people toward an appreciation of the relation between feces and disease. In this work schistosomiasis would be only one of several diseases requiring emphasis, but its severe clinical effects and its relation to the snail make it an appropriate disease on which first to focus the attention of an ignorant population.

Conclusions.

1. The problem of prophylaxis of schistosomiasis japonica is one of great magnitude and is very important to the rice-growing regions of China.

2. It seems unwise at the present time to adopt for China the method now chiefly used in Japan for eradicating the disease, that is, the extermination of the intermediate host. The extent of distribution of the snail makes this method hopeless, unless a natural enemy of the snail can be introduced to kill it.

3. It seems unwise at the present time to abandon all other methods of attack in favor of general therapeutic prophylaxis, such as exists in Egypt, but this method may be used to great advantage in the general prophylaxis problem.

4. The most effective methods will be those in which the population of the endemic regions cooperate. Such cooperation must be secured, for the present, by educational means. Governmental aid in enforcing public health measures may possibly be obtained at a later time.

5. We recommend the following prophylactic measures for China in the order of their importance, as the present analysis of the problem justifies:

(*a*) The control of feces disposal.

(*b*) The avoidance of wading in canals, ponds, small lakes and irrigation ditches, and the protection of the skin by workers in rice nursery beds.

(*c*) Extensive specific treatment of the disease in out-patient clinics by all qualified hospitals in endemic regions.

6. Immediate steps should be taken to start prophylactic measures against this disease. The activities which will contribute most to the progress of prophylaxis are: (1) More accurate determination of the distribution of the disease and of its intermediate hosts. (2) Intensive study of, and experimentation in prophylaxis in small areas. (3) Demonstrations of specific treatment. (4) Educational propaganda throughout all known and suspected endemic regions.

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EXPLANATION OF FIGURES. (PLATES XXXIV AND XXXV.)

FIG. 1. Native worker near El Marg, Egypt, operating spiral water lift, with legs constantly immersed in "infected water." The man was "caught" scratching his legs which were itching from attacks of cercariae.

FIG. 2. Infected canal passing through the village El Marg. This is both the sewer and water supply for the city.

FIG. 3. The canal passing the village mosque at El Marg. The night soil drain from the back of the mosque flows into the canal. Just beyond this point women on the bank were washing their clothes.

FIG. 4. The canal near the date grove, just north of El Marg, in which the mollusc Isadora (Bullinus) was found in large numbers.

FIG. 5. Farmer transplanting rice in Central China.

FIG. 6. Water-wheel operated by water-buffalo near El Marg. For a similar method of drawing water in China, compare Plate XVI, Fig. 2.

FIG. 7. Compound foot-tread for raising water from the main canals to the rice fields.

FIG. 8. Simple foot-tread for raising water from subsidiary canals to the rice fields.

FIG. 9. A common type of small village "kang" for use in ripening human excreta.

FIG. 10. Stone cesspit used in some localities in Central China for ripening human excreta.

FIG. 11. Ordinary "sampans," common throughout Central and South China.

FIG. 12. Small house-boat of the type used in Chekiang Province, China.

Fig. 1

Fig. 2

Fig. 3

Fig. 4

Fig. 5

Fig. 6

(Faust and Meleney: Studies on Schistosomiasis Japonica, VIII.)

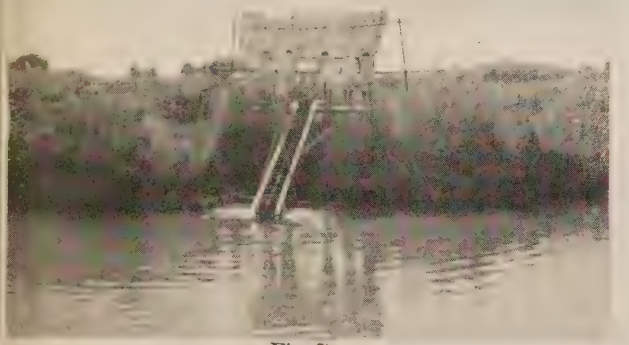


Fig. 7

Fig. 8

Fig. 9

Fig. 10

Fig. 11

Fig. 12

skill, and last, but not the least, to Babu D. N. Bagchi, who has prepared under my supervision the excellent photographs of shells and the drawings of radulae, etc., here reproduced.

Technique.

My plate consists of reproductions of practically untouched photographic prints from negatives taken direct through a magnifying lens (Leitz's) with a vertical camera. The shells were fixed in position on a clean glass plate with a minute fragment of plasticene, and a piece of blue paper was placed some inches below the glass. A very small stop, with an aperture only 1 mm. in diameter, was used in the lens. The use of a glass plate, supported some distance above either a blue or a black background (in accordance with the color of the object to be photographed), is a device in the photography of small macroscopic objects well known to photographers, but by no means so universally known among zoologists as it should be. It eliminates all shadows cast by the object, and thus renders it possible to obtain a much clearer and more definite outline.

As my paper is written for a medical publication, I propose to divide it into two parts, the first on the practical diagnosis of the disease-carrying species, the second a technical description of the carriers and of the forms that have been confused with them. In the latter I have quoted the original descriptions of species freely.

Part I. Practical Diagnosis of the Species.

In this part of the paper I will give a general description of the shells and animals of the snails, convicted or suspected, on good evidence, of being the molluscan hosts of *Schistosoma japonicum* and of the forms with which they are liable to be confused. It is written rather for the sanitarian than for the malacologist.

The known and suspected hosts all belong to a single genus for which the correct name in my opinion is *Oncomelania* Gredler, but this genus may conveniently be divided into two sections, for which the name *Katayamae* and *Hemibiae* may be used.

The shells in both sections are long and narrow, with many whorls and with the breadth increasing gradually from the apex downwards. The basal whorl is never much broader than the one above it, and the apex of the shell, when it is not worn away, is fairly sharp. The sculpture of the surface is arranged in vertical, not spiral or transverse lines. The mouth of the shell is ovate, pointed above and broadly rounded below. Its outer lip is sharp, but just outside it, on the

external surface, there is a coarse ridge or varix, with which a thickening corresponds on the internal surface. The shell in all known living forms is between 6 mm. and 12 mm. high, and considerably more than twice as high as it is broad at the base. Its color is always dull and uniform. The operculum which closes the shell is very thin and transparent, of ovate outline and with a small spiral figure on the inner side towards the base.

The animal has a short, blunt snout, bilobed in front and not very extensile: it does not pull itself along by means of the snout. It has, on either side of its head, a thin tapering tentacle and its eyes are situated on the sides of the head near the base of the tentacles. The foot on which the animal crawls is broad and short, rounded behind and truncate in front. The antero-lateral angles are rounded and not produced into distinct processes or even sharp angles.

The two sections of the genus are distinguished by the fact that in the *Hemibiae* there are stout, convex, smooth, vertical ribs on the surface of the shell, while in the *Katayamae* these ribs are replaced by faint lines, which leave the surface almost smooth.

All the species live in damp places, but not in water, and bury themselves in the earth when climatic conditions are unfavorable.

As all the species of this genus are probably potential hosts of the human blood-fluke in China, Japan or Formosa, it is important that they should be distinguished readily from other snails which are, so far as we know, harmless, but are found in the same districts, and look more or less like the true hosts.

In China this seems to be easy enough. Dr. Faust has shown me two species with which he considers confusion possible. One of these is a true land snail of the genus *Opeas*, apparently a race of the widely distributed *O. gracile* (Hutton), a species originally described from India, but distributed over the tropics of both hemispheres. Allied species occur in different parts of China. The shell may be distinguished from that of any *Oncomelania* by its very pale color and by the fine, regular, vertical striae on its surface. There is no thickening round the mouth, and the whole structure is different microscopically. The animal is even more different than the shell. Its eyes are borne at the end of slender, tentacle-like stalks and can be retracted into the head, while there is a pair of short, almost tubercle-like, true tentacles in front of the eye-stalks. *There is no operculum.*

There is perhaps more likelihood of confusion with small specimens of the water-snail *Melania* (*Semisulcospira*) *cancellata* (Benson) (Pl. XXXVI, Figs. 18, 19) of the family Melaniidae (Tiaridae), which is

very common in muddy water all over the plains of eastern and central China, except in the extreme north. Apart from the fact that this species is aquatic in habits, it may be distinguished by the following characters: (*a*) it is much larger than any species of *Oncomelania*, (*b*) the lip of the shell is very thin and somewhat serrated, (*c*) there are several smooth spiral ridges at the base of the shell and (*d*) the vertical ribs on the shell, which give it its resemblance to species of *Oncomelania*, of the section *Hemibiae*, are traversed by numerous horizontal grooves.

In Yünnan and Szechuan small species of the genus *Tricula* Benson (*Hypsobia* Heude) occur which are liable to be confused with the smooth forms of *Oncomelania*, to which they are related. Their shell, however, is smaller than that of any species of *Oncomelania* (less than 5 mm. high) and can be easily distinguished by the absence of a varix on the lip. No species of *Oncomelania*, moreover, is known from these provinces, although the presence of schistosomiasis japonica has been established for the central Szechuan plain.*

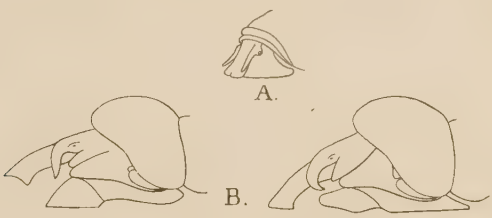
In the great lakes of Yünnan, the family to which *Oncomelania* belongs is apparently replaced by another (the Delavayidae), some species of which have shells not unlike those of *Oncomelania*. They have no varix, however, and their sculpture is spiral, not vertical. Their anatomy differs widely. These shells belong to the genera *Delavaya*, *Paraprososthenia* and *Parapyrgula*.

No species of *Oncomelania* has been recorded from French Indo-China as such, but the genus *Pachydrobia* is similar in some respects, and some of the species hitherto assigned to it are probably true *Oncomelaniae*. The shells in the true *Pachydrobia* are much broader and more conoidal and never have stout vertical ribs. The gill-filaments also appear to be much shorter and the antero-lateral angles of the foot more acute (Fig. 3). *Pachydrobia* is aquatic. All other allied genera found in China may be distinguished from *Oncomelania* by their thick calcareous operculum, which is marked externally with concentric lines.

In Japan it is much more difficult to recognize *Oncomelania* with certainty, for another genus exists in that country which resembles it very closely so far as the shell and operculum are concerned, and also in habits, but differs from it widely in anatomy. The resemblance is so close that it has deceived one of the most distinguished of living conchologists. This genus is *Blanfordia*. The shell is very similar in every respect but three to that of *Oncomelania* (section *Katayama*).

* It seems possible that Heude's reference to his *Hemibia costulata* (= *Oncomelania hupensis?*) "from the upper Yangtze" may mean Szechuan. E. C. F.

The points of difference are: (*a*) that the apex of the shell of *Blanfordia*, even when complete, is blunt and flat, (*b*) that although there is usually a varix on the outside of the lip, there is no thickening on the inner surface and (*c*) the number of whorls is smaller. The differences in the animals are much greater, that of *Blanfordia* being highly modified in accordance with a peculiar mode of progression. The snout is much longer and relatively narrower than that of *Oncomelania* and is highly extensile, forming a regular proboscis, while the foot is divided by a transverse furrow into two parts, which are capable of independent movement. The snail, instead of gliding evenly on its foot, moves something like a leech, dragging itself forward by means of its snout, the tip of which is applied to the ground, and pressing down the two parts of its foot separately.



TEXT–FIG. 1. *Oncomelania* and *Pomatiopsis* crawling. *A*, *O. hupensis* (after Heude). *B*, *P. lapidaria* (after Stimpson).

I reproduce here figures (Fig. 1) of the living animal of *Oncomelania* and of *Pomatiopsis*, an American genus, closely allied to *Blanfordia*, of the animal of which no figure or material for a figure is available. According to Adams, *Blanfordia* has flattened triangular tentacles, but is otherwise similar in external anatomy to *Pomatiopsis*. Stimpson's figure of the latter, however, shows a triangular process behind the true tentacle.

The species of *Blanfordia* live like those of *Oncomelania* in damp places near water, but I have found no record of their occurrence in exactly the same localities.

According to Cort (1920: 88) the resistance to desiccation of *O. nosophora* is limited to about three months, but it is possible that *O. hupensis* hibernates for longer periods in the earth. I found no specimens of this species near the Tai Hu (Great Lake) in December, although it is abundant there in March, when it seems to be just emerging from its winter sleep (*fide* Faust). It is, therefore, useless to look for the mollusc in winter, at any rate above ground.

Part II. Taxonomy of the Triculinae and Pomatiopsinae.

In this part of the paper I have placed the two subfamilies discussed in the family Rissoidae. Some justification is necessary for adopting this course, as it is a return to an old-fashioned classification. In recent times most malacologists have separated the freshwater forms of this assemblage (under the names Hydrobiidae, Paludestrinidae or Amnicolidae) from the *Rissoidae* (*s.s.*), which are mainly marine, but include a number of estuarine forms. The separation is not justified by any important conchological or anatomical difference, and even ecologically has little to recommend it in view of the large number of species found in brackish water. I think it best, therefore, to use the name Rissoidae in a broad sense and to recognize a considerable number of subfamilies.

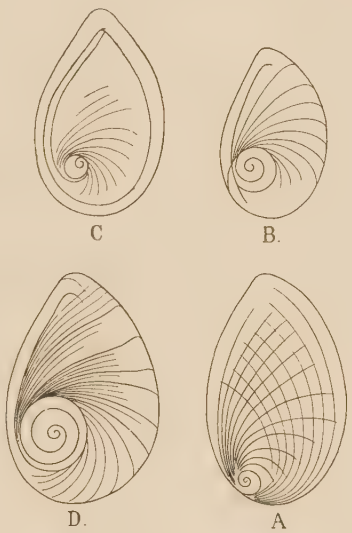
This procedure is the more to be recommended in that there is considerable doubt as to the proper family name of the freshwater forms, if they are kept in a distinct family. The name Hydrobiidae was used for many years, but has now been generally abandoned, on the ground of priority, the name *Hydrobia* (molluscs) being preoccupied in beetles. Most European authors have adopted "Paludestrinidae" (Newton, 1891: 226) in its stead, and American authors "Amnicolidae" (Walker, 1918: 27). *Paludestrina* d'Orb. (1840) has, according to experts on nomenclature, a year's priority over *Amnicola* G. and H. (1841), but the objection to the use of the former in its patronymic form is that it was originally given to obscure species of which the true affinities are unknown. Moreover, *Lithoglyphus* has apparent priority and "Amnicolinae" was adopted as a subfamily name by Gill as long ago as 1871. In this I follow Gill. *Paludestrina*, in any case, must belong to a different subfamily from *Tricula*, if, at any rate, accepted generic identifications are correct. Walker includes it among the Amnicolinae (1918: 29).

The only family among the freshwater Gastropods of China and neighboring countries with which the Rissoidae migh tbe confused are the Delavayidae of the lakes of Yünnan. This family, which I regard now as distinct from any other, consists of the genera *Delavaya* and *Fenouilia* Heude, *Paraprososthenia* Annandale and *Parapyrgula* Annandale and Prashad. The genera have been discussed by Dr. Prashad and myself (1919 (*a*): 413), but I find that the radula of *Delavaya* is quite distinct from that of *Parapyrgula* and therefore now accept them as distinct genera. The family is distinguished by the absence of a copulatory organ in the male and by the fact that the central tooth of the radula has a single undivided cusp, while the

denticulation of the laterals is also much reduced. It is related to the American Pleuroceratidae. The Cambodian genus *Lacunopsis* Deshayes perhaps belongs to it, but otherwise it is known only from Yünnan.

Family Rissoidae.

The family consists of small or very small pectinibranchiate Gastropod molluscs with a conical or subspherical shell which is rarely very thick and rarely exceeds 10 mm. in length.* The snout is more or less extensile, but there is rarely an introverted proboscis. The jaws are tessellated, being composed of minute columnar bodies. The radula has the formula 2.1.1.1.2. All the teeth have several denticulations on the cusp and one of these is usually enlarged on the central and the laterals. Denticles on the disc of the central are present or absent. The laterals and marginals are not provided with membranous expansions on the outer margin and the laterals have not a separate basal plate. The foot is longer than broad, truncate in front and pointed or narrowly rounded behind. Its sole is not divided longitudinally. The gills consist of distinct filaments without anastomosis. The male intromittent organ ("verge") is external and neither of the tentacles possesses sexual characters. The edge of the mantle is smooth. The blood, so far as is known, is colorless.



Text–fig. 2. Opercula of Triculinae and Pomatiopsinae. *A*, *Tricula gregoriana*. *B*, *Oncomelania formosana*. *C*, *O. hupensis*. *D*, *Blanfordia japonica*.

In the inland waters of the territory under consideration no less than five subfamilies may be distinguished, as follows:

I. Shell lenticular, compressed dorso-ventrally. Operculum with two transverse ridges on the internal surface. Antero-lateral angles and often apex of foot produced . . . . . *Stenothyrinae.*

II. These characters absent.

A. Shell subspherical, with the body-whorl greatly enlarged and with the spire small . . . . . *Lithoglyphinae.*

* One of the few exceptions is my *Pseudovivipara hypocrites* from Kiangsu (Annandale, 1918: 309). In this species the shell is 17.5 mm. high.

B. Shell conical, conoidal or turrited, tapering.
1. Operculum thin, horny, small, capable of retraction into shell.
a. Foot divided by a transverse furrow..... *Pomatiopsinae.*
b. Foot simple..... *Triculinae.*
2. Operculum thick, calcareous, incapable of retraction into the shell..... *Amnicolinae.*

This key refers only to the forms that occur in southern and eastern Asia. *Amnicola* (*s.s.*), which is American, with one problematic species in northwestern India, has a horny, spiral operculum, but in the Oriental subgenus *Alocinma* the operculum, though similar in structure, is calcareous, and *Alocinma*, again, is very closely related to another Oriental and Chinese genus (*Hydrobioides*) in which the operculum is concentric in the adult, but spiral in the young. *Alocinma* occurs in Formosa. The Chinese and Japanese genera of the subfamily all have concentric opercula.

I do not regard the Lithoglyphinae as a natural assemblage, but the grouping is convenient for purposes of identification.

Subfamily Triculinae nov.

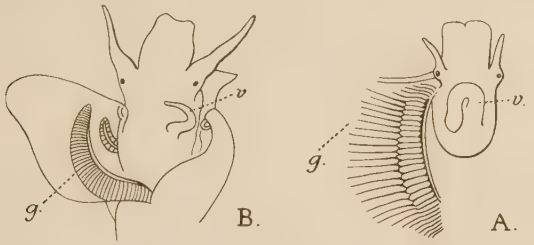
The members of this family are small or of moderate size, the shells rarely attaining a length of 10 mm. They are always elongate and have a considerable number of whorls. The operculum is thin, transparent and paucispiral. The radular teeth have none of the denticulations greatly enlarged, and all the denticulations are relatively broad; the central bears two or three lateral denticulations on each side of the disc. The foot is simple and undivided and neither its apex nor its antero-lateral angles are produced. The snout is comparatively short and broad, but longer than in some allied forms. The tentacles are filiform and the eyes lie on the sides of the head near their base. The gill-filaments are usually prolonged across the roof of the mantle cavity to the anal border (except probably in *Pachydrobia*), but the true gills, which are expanded and bear long cilia, are reduced in length relative to that of the paractenidial filaments. In the central nervous system the longitudinal commissures are relatively long and the whole structure has a discrete appearance. The verge does not have a lateral appendage.

In the territory of which I am writing four genera occur which may be distinguished as follows:

A. Shell with the lip thickened.
1. Shell conoidal, not turrited..... *Pachydrobia.*
2. Shell turrited, elongate..... *Oncomelania.*

B. Lip thin.

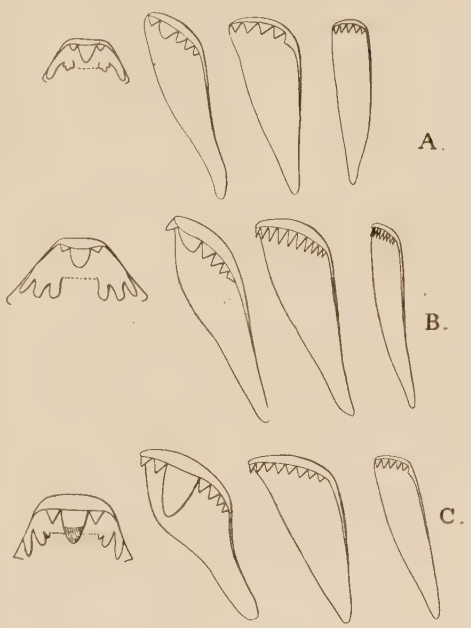
1. Shell pigmented, smooth . . . . . *Tricula.*
2. Shell unpigmented, hyaline, with fine vertical and spiral sculpture . . . . . *Taihua.*



TEXT–FIG. 3. Head, etc., of *Oncomelania* and *Pachydrobia*. *A*, *O. hupensis* (after Heude). *P. paradoxa* (after Poirier). (N.B. The two figures are not drawn from exactly the same point of view, but they show the greater comparative length and extent of the gill-filaments in *Oncomelania* and the projecting surfaces of the true gills.) *g* = gill. *v* = verge.

Of these genera *Pachydrobia* Crosse and Fischer is Indo-Chinese, but occurs in the extreme south of China. Bavay and Dautzenberg consider *Oncomelania* identical with it (1912: 34), and it is possible that some species, referred to it, actually belong to *Oncomelania*, but the animal of the true *Pachydrobia* (Poirier, 1881, Pl. iii) seems to differ, especially in the structure of the gills (Text-fig. 3).

The other genera are distributed in our territory as follows: *Oncomelania* occurs all over China, except in the extreme northern and western (?) provinces. Its precise distribution calls for investigation. *Tricula* has been found in China, only in the provinces of Yünnan and Szechuan, *Taihua* only in the Tai-hu (Great Lake) in Kiangsu.



TEXT–FIG. 4. Radulae of *Tricula* and *Oncomelania*. *A*, *T. montana* (from one of the paratypes). *B*, *O. nosophora*. *C*, *O. formosana*. All the figures × 500.

In Japan *Oncomelania* is confined to the southern half of the archipelago, in which its distribution appears to be somewhat sporadic. It also occurs in Formosa.

Genus **Tricula** Benson (1843).

Tricula Benson, 1843: 467.
Hypsobia Heude, 1890: 173.
Tricula Prashad, 1921: 67.

This genus was described from the Himalayas by Benson in 1843 and redescribed in 1890 by Heude from China. Hitherto I have regarded the European genus *Bithinella* Moquin-Tandon (1851: 239, and 1855: 516, Pl. xxxviii) as synonymous with it, but an examination of the radula of the type-species (*T. montana* Benson), and a comparison in detail of Heude's figures with those of Moquin-Tandon and Bregenzer (1916: 237), as well as of the actual operculum with these figures, renders this generic identity impossible.

The difficulties are (1) that the spire of the operculum coils the opposite way in *Bithinella* from *Tricula* (2) the central tooth of the radula is produced into lateral processes in *Bithinella* and merges gradually into the lingual membrane in *Tricula;* (3) this tooth has only one basal denticle on each side of its disc in *Bithinella* and two or three denticles on each side in *Tricula;* and (4) the verge is simple in *Tricula*, but bears a lateral appendage and a flagellum in *Bithinella*. This last character is distinctly of generic importance.

Tricula may be defined as consisting of small, often minute Triculinae with elongate-ovate, acuminate shells, which possess no varix, but are slightly thickened inside the lip. The peristome is complete and ridge-like, more or less detached from the body-whorl and never expanded or thickened; the mouth of the shell is never trumpet-shaped. The umbilicus is closed or rimate. There is no prominent shell-sculpture. The protoconch is minutely mammillate and the apex of the shell not very acute. The operculum has the nucleus close to the base of the inner margin and is ornamented with very fine curved lines, often crossing one another in opposite directions; its spire coils from right to left. The central tooth of the radula has two or three lateral denticles on each side of the disc, and its basal angles are not produced.

Type-species: Tricula montana Benson.

It is still uncertain whether some or all of the species from western Asia assigned to *Bithinella* belong to this genus, which has been defi-

nitely recorded from the western Himalayas, the hills of Assam, the plains of peninsular India (Prashad, 1921), the western provinces of China and the Philippines (Quadras and Möllendorff, 1915). I have seen fresh specimens from Bombay and Sind in western India and subfossil shells from the South Shan States in Burma. Doubtless the small size and inconspicuous appearance of the shells have caused them to be overlooked in many places.

I figure the radular teeth of one of Benson's original specimens of *T. montana* (Text-fig. 4*A*). They agree closely in most respects with Heude's figures of those of *T. humida* from Szechuan, but the central has only two instead of three basal denticles on each side and is relatively narrower.

Two species of this genus are now known from western China, namely *T. humida* (Heude) and a new species, here described from Yünnan under the name *T. gregoriana*. *Oncomelania* is probably an offshoot from *Tricula* which has been evolved in central or eastern China under particularly favorable conditions, but its original home may have been the Shan plateau in Upper Burma, where fossil species have been found.

Most of the species of *Tricula* seem to be aquatic and to live among stones or weeds in very shallow water, either in mountain streams or at the edge of rivers. *T. humida* was found on wet rocks and *T. gregoriana* at the base of a high cliff, probably at a place where water dripped from above. I have found *Lymnaea truncatula*, a member of an aquatic genus, in similar conditions in both the Hebrides and the Riviera. There is no evidence that the species of this genus transmit disease.

Tricula humida (Heude) (1890).

Hypsobia humida Heude, 1890: 173, Pl. xxxiii, Figs. 12, 12*a*, 12*b*.

The species is only known from Heude's figures and description. It is possible that it was founded on abnormal, subscalariform individuals, for its main characteristics are the obliquity of the spire, the depth, breadth and irregularity of the suture and the consequent complete detachment of the peristome from the body-whorl. The radula, as figured by Heude, has three basal denticulations on each side of the disc of the central, whereas the type-species has two. Otherwise it is not discrepant.

The species was described from Chengtu, Szechuan.

Tricula gregoriana, sp. nov.

(Plate XXXVI, Figs. 1, 2.)

The shell is larger than that of the type-species (4.5 mm. x 2 mm.) and of elongate, narrowly ovate form. The protoconch is small and mammillate. There are 5½ whorls, which increase in size gradually and evenly. They are slightly convex, but not at all swollen. The body-whorl is a little oblique and its height on the dorsal surface is approximately equal to that of the two whorls above it. It exhibits no sign of angulation, but is evenly convex in profile. The suture is oblique and linear, with the whorls very narrowly flattened outside it. The mouth is pyriform and oblique, with the peristome linear and hardly detached from the body-whorl. It projects very little in ventral view and is longer than the part of the body-whorl above it on the outer side. The lip is sinuate in lateral view. The columella is arched and practically without a callus. The umbilicus is narrowly rimate. The natural color is pale fulvous, but the surface is covered with a thin black deposit in the specimens examined. This obscures the microscopic sculpture, which consists of rather coarse, but regular vertical lines, set far apart.

Unfortunately the remains of the animal have been completely destroyed by mould, but I figure the operculum (Text-fig. 2*A*).

The species is described from several specimens taken by Professor J. W. Gregory, of Glasgow University, at the base of a cliff, above the Awa bend of the Upper Mekong, in western Yünnan, at an altitude of 6,400 feet.

The type-specimen is preserved in the Indian Museum and paratypes have been sent to the British Museum.

Taihua, genus nov.

Hypsobia (in part) Annandale, 1918, p. 306.

The shell is minute, fragile, hyaline and colorless, with many whorls, which increase in size very gradually towards the base, which is contracted. It has a minute spiral and longitudinal sculpture. The mouth is suboval, slightly contracted, with a complete peristome and a very thin outer lip. There is no trace of a varix. The umbilicus is closed and the columellar fold thin, narrow and simple. The operculum is broadly ovate, sinuate on the inner margin, extremely thin and transparent, but apparently calcareous. Its nucleus is situated in the lower half, near the inner margin, and is surrounded by a simple spiral line of only two turns. The outer part is decorated with several curved longitudinal rows of short transverse lines.

The tentacles are filiform, and the eyes, which are situated in the usual position at their base, very small. The foot is simple and the snout rather slender. The male organ is blunt and rather short, without a lateral appendage.

The only known species is *T. minuscula* (Annandale), which was dredged in large numbers at one spot from the muddy bottom of the Tai-hu (Great Lake) in Kiangsu in December, 1915. It occurred in about 3 meters of water and is thus evidently an aquatic species. The type-specimen is in the Indian Museum.

There is no evidence that this species transmits disease.

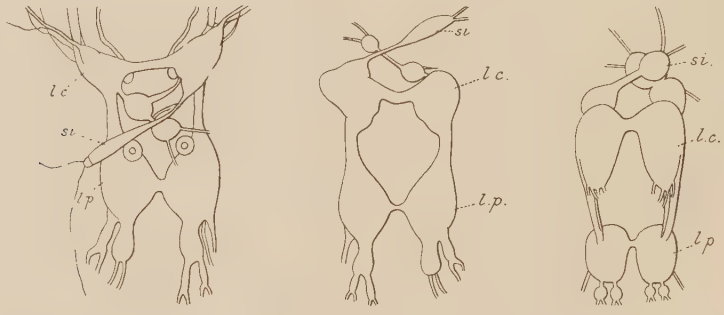
Genus **Oncomelania** Gredler (1881).

Oncomelania Gredler, 1881: 120.
Hemibia Heude, 1889: 47.
Hemibiae Heude, 1890: 167.
(Plate XXXVI).

I have already mentioned (p. 276) the conchological characters whereby this genus may be distinguished from *Tricula*. I have only to add that the protoconch, though not broadly expanded as in *Blanfordia*, is flatter and has a wider suture than in *Tricula*. The operculum has the nucleus further from the base of the shell, but is otherwise similar. The radula is identical.

Robson claims that the structure of the central nervous system differs, if Heude's figure be correct, in *Katayama* and *Oncomelania* (*Hemibia*), but on detailed comparison of his figure with Heude's the differences do not seem to me more than specific, allowance being made for the fact that the two figures are drawn from different points of view, and that in Heude's the structures have been artificially displayed. The real differences between the "brains" of *Katayama* and *Oncomelania* are precisely similar to those between the "brains" of different species of *Vivipara* (Annandale and Sewell, 1921: 237, 269) and of *Taia*, the anatomical differences between the different species of which I hope to discuss elsewhere shortly. They come to this, that in different species certain ganglia may be either fused together or connected by a short, stout commissure or by a much longer and narrower one. This point is discussed in further detail later. I give reproductions here (Text-fig. 5), in outline, of part of Heude's and of Robson's figures drawn to scale. I have also attempted to transpose the former, so as to show the structures in the view in which they are shown in the latter. This transposed figure is necessarily somewhat

diagrammatic, but it gives the relationships of the different ganglia and commissures with sufficient accuracy and explains my description in the text.



TEXT–FIG. 5. "Brain" of *Oncomelania*. *A*, *O. nosophora* (dorsal view, after Robson). *B*, *O. hupensis* (ventral view, after Heude). *C*, Transposed figure of the latter, showing (approximately) the dorsal view. The nerves arising from the dorsal surface of the ganglia are necessarily omitted. *l.c.* = left cerebral ganglion. *l.p.* = left pedal ganglion. *si.* = supraintestinal ganglion.

I can find no other anatomical difference between the two sections that seems to me more than specific and the shells of Heude's *Hemibia* and of Robson's *Katayama* are linked together by the form called *H. sublaevis* by the former author. I regard the *Hemibiae* and the *Katayamae*, therefore, as mere sections of *Oncomelania*, distinguished by the fact that the shells of the species included in the *Hemibiae* have vertical ribs and those included in the *Katayamae* have not.

For the present we must recognize five living species of *Oncomelania*, distinguishing them as follows:

I. Shell smooth (*Katayamae*).
  A. Complete shell less than three times as high as it is broad. *O. formosana.*
  B. Complete shell more than three times as high as it is broad. *O. nosophora.*
II. Shell with vertical ribs (*Hemibiae*).
  A. Ribs by no means prominent ..... *O. sublaevis.*
  B. Ribs prominent.
    i. Shell more than 9 mm. high ..... *O. longiscata.*
    ii. Shell less than 8 mm. high ..... *O. hupensis.*

O. sublaevis and *O. longiscata* are doubtful species, only known from Heude's figures and descriptions. All the rest, figured by him, I include under the name *O. hupensis*. The supposed species *schmackeri* is to be attributed to Boettger, who described it as a *Melania*, and not to Möllendorff. The Cambodian species "*Pachydrobia*"

harmandi, *P. variabilis* and *P. scalaroides* Poirier (1881, Pl. ii) probably belong to the genus *Oncomelania*, but nothing is known of their anatomy. They may be distinguished from the Chinese species of the section *Hemibiae* by the fact that the ribs on their shells do not extend down to the base of the whorls. The shell in *P. scalaroides* is also much broader than that of any Chinese form.

In addition to these living forms several fossil (tertiary) species have been described from Burma (Annandale, 1919: 225, Pl. xxxii).

Probably all the living species of the genus are potential carriers of *Schistosoma japonicum*, but further information is needed on this point.

Section **Katayamae** Robson (1915).

Katayama Robson, 1915: 203.
Hypsobia (in part) Annandale, 1918: 306.
Hypsobia Robson, 1921: 402.

Of the two species of this section, *O. nosophora* has probably a wide range in the central and southern provinces of China and in the southern provinces of Japan proper; while *O. formosana* is only known from Formosa.

Oncomelania nosophora (Robson) (1915).

Katayama nosophora Robson, 1915: 203, Figs.
Blanfordia nosophora Pilsbry, 1915: 2, Fig. 2.
Hypsobia nosophora Robson, 1921: 402, Figs. (anatomy).

Robson's original description of the shell is as follows:

"*Shell*, with eight whorls (Fig. 7) (the last two unusually eroded), increasing gradually in size and exhibiting a moderately convex profile and a fairly well-marked suture to correspond. The general shape is acuminate. The peristome is continuous, of a rich chocolate-brown color, thickened and reflected upon the ventral and columellar lips. In the region of the peristome the body-whorl is abruptly extended and the transverse growth lines tend to assume the character of ribs. The color is light olivaceous brown, the body-whorl being occasionally straw-colored and the two spiral whorls very dark purplish black owing to erosion. The texture is horny and fairly solid. Irregular transverse growth lines cross the finely and irregularly granulated surface which in places occasionally exhibits, under a high power, a faint spiral sculpture.

"*Dimensions of shell.* Maximum height 8.5 mm.; maximum width 3.1 mm.; maximum width of aperture 2.75 mm."

There is considerable variation in the varix in this species. It may be a fairly sharp and not very prominent ridge or a broad, prominent, convex, polished crest. Shells with both types of varix occur together. It is probable that at one stage of growth, just before the new lip is formed, the ridge is altogether absent.

The central tooth of the radula (Fig. 4*B*) is broad and transverse; its denticulation formula is $\frac{5(2.1.2)}{3+3}$. The central denticulation of the cusp is only slightly enlarged and the second denticulation, on either side, is slightly larger than the outermost one. The three basal denticulations on either side are relatively large, situated close together and arranged in an oblique series. The lateral is broad in proportion to its length and has 6 subequal denticulations; the inner marginal has 7 and the outer marginal 10.

This is the only known carrier of *Schistosoma japonicum* in Japan and is probably the main, if not the only, carrier in certain districts of China, in which, as Dr. Faust informs me, it is found chiefly in mountainous regions. He has sent me specimens from Shaosing in Chekiang and tells me that it also occurs in the Canton area (at Fatshan). In Japan it is abundant in some parts of the island of Kyushu and the adjacent parts of the Main Island. I have examined specimens from Katayama in the Bingo province of the latter. These specimens are topotypes.

Oncomelania formosana (Pilsbry and Hirase, 1905).

Blanfordia formosana Pilsbry and Hirase, 1905: 750.

This species is distinguished from *O. nosophora* by its relatively shorter and broader shell. Pilsbry's original description is as follows:

"The shell is perforate, light brown, rather solid, turriteconic, the outlines of the spire straight, apex rather acute. Whorls 6¾, quite convex and parted by well-impressed sutures, smooth except for faint growth-lines. The last whorl has a rounded and rather strong crest or varix behind the outer lip. The aperture is ovate, brown within; peristome brown-edged, the columella concave and somewhat thickened, whitish. Length 7, diam. 3.25 mm., length of aperture with peristome 2.8 mm."

The apex when complete is even sharper than in *O. nosophora*.

The radula (Fig. 4*C*) differs from that of *O. nosophora* in the following points:

The central tooth is much higher in proportion to its breadth and is constricted in its upper half. Its denticulation formula is also different, namely $\frac{3(1.1.1)}{2+2}$. and the central denticulation of the cusp is relatively larger. The two basal cusps have their tips distinct in the form of small spines. The laterals have only 4 denticulations, of which the third is enlarged; the inner marginals have 5 or 6 and the outer marginals 4 or 5.

The species was described from Rōnō in southern Formosa. I have examined a large series of specimens from that island sent me by Mr. Bryant Walker.

Section **Hemibiae** Heude (1889).

This is the typical section of *Oncomelania* and, had it not already been given a name, might stand as "*Oncomelania sensu stricto.*" Its Chinese species, if they are really distinct, are closely allied to one another. Heude recognized, but with much doubt, no less than seven, of which I have retained three provisionally. Each of Heude's supposed species came from a different locality, but I find, with specimens of four of them, named by himself before me, that these four and apparently two others can be matched precisely or very nearly with shells from a series collected by Drs. Faust and Meleney at Soochow in Kiangsu. These shells have been named *Oncomelania hupensis* Gredler by Mr. Bryant Walker, with whom I am in agreement as to the identification. They include shells of two distinct types, one much broader at the base than the other; but this phenomenon, as Mr. Walker points out in a letter, is of not uncommon occurrence in fresh water Gastropods and may be due to differences in sex. Heude's Figure 19 shows the broader (? female) type, his Figure 18 the narrower (? male) type.

Oncomelania hupensis Gredler (1881).

(Plate XXXVI, Figs. 9, 10, 11.)

Oncomelania hupensis Gredler, 1881: 120, Pl. vi, Fig. 5.
Melania (? *Sulcospira*) *schmackeri* Boettger, 1886: 3.
Hemibia Schmackeri, H. hupensis, H. carectorum, H. luteola, H. crassa, H. costulata Heude, 1890: 168–170, Pl. xxxiii, Figs. 1–7 (anatomy), 15–20 (shells).

Gredler's original description is as follows:

> "*Testa rimata, turrito-conica, fortiter transversa*" (*i.e.*, vertically in the phraseology here adopted) "*costata, costis discontinuis*"

(interrupted by the suture), "*solidula, pellucida. Anfractus valde convexi. Apertura integra (haud effusa), oblongo-ovata, minuta. Peristoma continuum aut connexum, circum late sublabiatum, extus costa fortiori (varice), reflexa aut tumida, margini parallela superstructum, margine externo medio paulo latius, interno supra reflexo. Operculum corneum, tenue, subspiratum, vix differt ab operculo generis Melaniae.*"

Unfortunately I have no anatomical material and the animal has been extracted or devoured by fly-larvae in all the shells I have examined. The following particulars are taken from Heude's figures, which on analogy must be substantially correct.

The operculum has its nucleus near the center of its lower half and is broadly and regularly ovate, much like that of *Blanfordia japonica*.

The radula closely resembles that of *O. formosana* in all details visible.

The gill resembles that of *O. nosophora*, but the brain (Figs. 5*B*, 5*C*), of which Heude gives a ventral view, differs in the following characters: The pedal ganglia are longer and narrower and the cephalic ganglia much smaller; the right pleural ganglion is partially fused with the right cephalic ganglion, and the commissure between it and the supraintestinal ganglion is very long and slender. The commissure between the left pleural ganglion and the left cephalic ganglion, and that between the former and the subintestinal ganglion are also relatively long and slender.

The verge, according to Robson, is rather more slender than in *O. nosophora*.

These differences, which are all that can be detected from Robson's anatomical account, do not seem to me, as I have already stated, to be more than specific.

The species has been recorded under different names from various places in the provinces of Kiangsu, Anhwei, Chekiang, Hupeh and Hunan. It haunts the banks both of hill-streams and of canals in the plains and is probably the chief carrier of the human blood fluke in many parts of these provinces. Doubtless it will be found in other adjacent provinces also.

Precise records are as follows:*

KIANGSU. Neighborhood of the Tai-hu (*Heude, Meleney*); Chinkiang-fu (*Heude*); Nanking (*Heude*).

* The original records are in French romanization of Chinese without the Chinese character. In one or two instances, therefore, the exact English equivalent is problematical, which might slightly alter distribution by Provinces. E. C. F.

ANHWEI. Ningkuo-fu (*Heude*).
KIANGSI. Tungliū lake (*Heude*).
CHEKIANG. Kashing (*Faust*); Sungkiang-fu (*Heude*).
HUPEH. Hankow (*Gredler*).
HUNAN. Tungting lake (*Heude*).
SZECHUAN (?). "Upper Yangtze" (*Heude*).

Oncomelania sublaevis (Heude) (1889).

Hemibia sublaevis Heude, 1890, p. 168, Pl. xxxiii, Fig. 15.

The only distinctive character, shown by Heude, is the obsolescent ribs on the shell. The species was found on the walls of a cave "in rivulis Ning-kuo hien" (Ningkuo-fu, Anhwei).

Oncomelania longiscata (Heude) (1889).

Hemibia longiscata Heude, 1890, Pl. xxxiii, Fig. 20.

According to the line printed with Heude's figure, this form is much larger than any other. The shell appears to be slightly over 10 mm. high. It was collected by Heude himself at the upper end of Tungting Lake, opposite the city of Chinchow (Hunan?).

Subfamily POMATIOPSINAE.

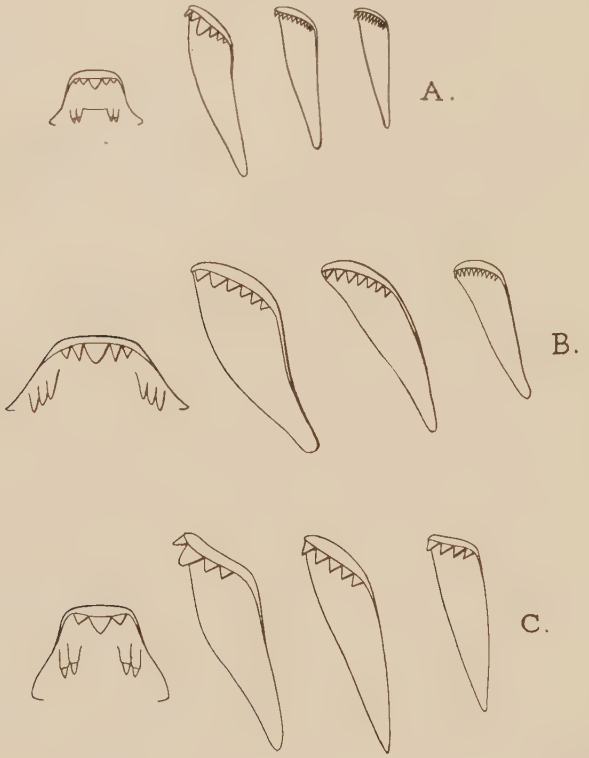
Closely as the shells of certain species of this subfamily resemble those of certain species of *Oncomelania*, the animals are strikingly different—so different that it may be necessary when the internal anatomy is known to separate the two genera *Pomatiopsis* and *Blanfordia* as a distinct family (*cf.* Gill, 1871: 7). The method of progression and the external peculiarities have already been described and also the essential differences between the shells of *Blanfordia* and *Oncomelania* (p. 273).

The Pomatiopsinae consist, so far as we know, of the two genera *Pomatiopsis* Tryon, which is widely distributed in North America (Stimpson, 1865: 29; Walker, 1918: 34), and *Blanfordia* Adams, which is restricted to the northern and central islands of Japan proper. The two genera seem to be closely allied, but the internal anatomy of both is unknown. The shells may be distinguished as follows:

1. Shell truncate, with at least traces of a varix on the outer lip..... *Blanfordia.*
2. Shell acuminate, without a varix; lip thin..... *Pomatiopsis.*

There is also a slight difference in the radula, at any rate, between the type-species of the two genera. In both, the central tooth has a

relatively large lateral denticle on each lateral margin and a distinct ridge across the center of the disc, but while in *Pomatiopsis lapidaria* there is at each end of this ridge a minute trilobed denticle, in *Blanfordia japonica* (and also in *B. bensoni*) there is a pair of relatively



TEXT–FIG. 6. Radulae of *Pomatiopsis* and *Blanfordia*. *A*, *P. lapidaria*. *B*, *B. bensoni* var. *hirasei*. *C*, *B. japonica* (from specimen named by A. Adams). All figures × *ca.* 330.

large elongate denticles in his position. We may express the difference thus: the denticulation formula of the central of *Pomatiopsis* is $\frac{5(2.1.2)}{1.1(3) + 1.1(3)}$ and that of *Blanfordia* $\frac{5(2.1.2)}{1.2 + 1.2}$. The upper line represents the denticulations of the cusp, the central denticulation being enlarged and thus differentiated from the other, while the lower line represents the denticles present on the disc. A reference to Text-fig. 6*A* will make this matter quite clear. The outer marginal in both genera is relatively larger than in *Oncomelania* and *Tricula*.

I need say nothing more about *Pomatiopsis* but must discuss *Blanfordia* in some detail.

There is no evidence that either species is a disease-carrier

Genus **Blanfordia** A. Adams (1863).

Tomichia A. Adams (not Benson), 1861: 308.
Blanfordia A. Adams, 1863: 424.
Pomatiopsis (in part) Pilsbry, 1900: 12.
Blanfordia (in part) Pilsbry, 1915: 1.

Actual confusion has occurred, as I have already stated, between this genus and the smooth-shelled forms of *Oncomelania*. Even Pilsbry, one of the most distinguished and experienced of conchologists, has included *O. nosophora* in his revision of *Blanfordia*, while Bartsch is reported to have gone still further and to have stated that the fluke-carrier of Japan was specifically identical with *B. japonica* (*Jour. Parasit.* 3: 182; 1917). I trust that my photographs will serve to correct this error.

Apart from the species *nosophora* Pilsbry (1915) recognized three Japanese species of *Blanfordia*. Unfortunately he does not seem to have seen any of Adams's original material and has thus been led into error, for Adams gave no figure of his two species, *B. japonica* and *B. bensoni*. I have been more fortunate in this respect, for the Indian Museum possesses several specimens of the former species and one of the latter, labelled in their author's own handwriting and doubtless presented by him to the late Dr. W. T. Blanford, after whom the genus was named. These specimens prove that the synonymy has been much confused. The species described by Pilsbry as *B. japonica* is not the true *japonica*, and neither is the form he named *B. bensoni* the typical *bensoni*, with which his *B. simplex* is identical. It therefore becomes necessary to find a new name for Pilsbry's (not Adams's) *japonica* and to suppress his *simplex*. The form he called *bensoni*, for which the name *hirasei* is available, is, however, in my opinion merely a large, well-developed variety of the true *bensoni*. I recognize in the genus, therefore, three species and a variety, which may be distinguished as follows:

1. Shell with varix on lip very strongly developed; apex broadly truncate.
   A. Breadth of apex contained 4 to 5 times in the greatest transverse diameter of the shell. Varix very broad, concave on the surface, extending round the mouth of the shell to the umbilicus..... *B. japonica.*

B. Breath of apex contained 9 times in the greatest transverse diameter. Varix much less well developed, not extending round the mouth of the shell	*B. pilsbryana.*
2. Varix much less well developed; breadth of apex of shell contained about 10 times in the greatest transverse diameter.	
A. Shell 5–6 mm. high, with $5\frac{1}{2}$ whorls	*B. bensoni.*
B. Shell at least 8 mm. high, with more than 5 complete whorls	*B. bensoni* var. *hirasei.*

Blanfordia japonica (A. Adams) (1861).

(Plate XXXVI, Figs. 15, 16, 17.)

Tomichia japonica Adams, 1861: 308.
Blanfordia japonica Adams, 1863: 424.

Adams's original description of the shell is as follows: *testa rimata, epidermide olivacea obtecta; spira elata, apice truncato; anfractibus 3½, convexiusculis, longitudinaliter strigosis lineis virido-fuscis transversis ornatis; apertura ovato-elliptica; peristomate continuo, duplicato, interno, recto, subacuto, externo valde incrassato.*

The color is pale olivaceous with *vertical* streaks of olive green. The actual number of whorls is $4\frac{1}{2}$ to $5\frac{1}{2}$, for Adams evidently did not include the protoconch in his enumeration. The shell is so broadly truncate that it is practically barrel-shaped. The operculum is broadly ovate.

The lateral denticles of the central tooth of the radula (Text-fig. 6*C*) are larger than those on the disc, the outer of which is larger than the inner. There are 7 denticulations on the laterals, the fifth from the outer margin being greatly enlarged. The inner marginal has 8 denticulations and the outer 5.

This species is known only from the island of Sado, which lies some distance off the west coast of the Main Island of Japan.

Blanfordia pilsbryana nom. nov.

Blanfordia japonica Pilsbry (not Adams), 1915: 2, Figs. 1, 1*a*.

I have not seen this species, which is also from the island of Sado, but it is evident from Pilsbry's description and figures that the shell is much less barrel-shaped and that the varix is less highly developed and less extended than that of *B. japonica*. It seems to provide a link between *B. japonica* and *B. bensoni*, which are very distinct and might almost, if they stood alone, be separated generically.

Blanfordia bensoni (A. Adams) (1861).

Tomichia bensoni Adams, 1861: 308.
Blanfordia bensoni Adams, 1863: 424.
Blanfordia japonica var. *simplex* Pilsbry, 1902: 26.
Blanfordia simplex Pilsbry, 1915: 3, Figs. 3, 3*a*.

In complete shells of this form the apex is less broadly truncate than in the two preceding species, and the varix is almost vestigial. It can, however, be detected in a good light on shells which have completed their period of growth. Adams describes the species as follows: *testa rimata, epidermide rufo-fusca obtecta; spire elata, apice truncato; anfractibus* 4, *convexis longitudinaliter strigosis; apertura ovato-elliptica; peristomate continuo, incrassato, extus subvaricoso.*

There are actually $5\frac{1}{2}$ whorls. The operculum is narrower than in *B. japonica*.

This form seems to be widely distributed in Japan from Hokaido to Kyushu.

Var. **hirasei** (Pilsbry) (1900).

Pomatiopsis hirasei Pilsbry, 1900: 12.
Blanfordia bensoni Pilsbry, 1915: 2, Fig. 4.

This form seems to be merely a large variety of *bensoni*, probably with an extra whorl. I have examined several specimens from Inoshima, sent me by Mr. Hirasé some years ago, and have figured the radula here (Text-fig. 6*B*). In at least one of these shells the varix is no better developed than in the shell of the typical *B. bensoni*, figured on my plate.

The central tooth of the radula differs from that of *B. bensoni* in that the three denticles on each side of the disc are subequal and the central denticulation of the cusp less enlarged. The laterals have 6 denticulations, of which the fifth is moderately enlarged; the inner marginals have 10 and the outer marginals 8.

List of Literature.

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Annandale, N.
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HEUDE, P. M.

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MOQUIN–TANDON, A.

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NEWTON, N. BULLEN.

1891. Systematic list of . . . British oligocene and eocene mollusca in the British Museum. (Nomenclature.)

Pilsbry, H. A.

1900. Notices of some new Japanese molluscs. *Nautilus, 14*: 11. (Description of *Blanfordia bensoni* var. *hirasei*.)

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Pilsbry, H. A., and Hirasé, Y.

1905. Catalogue of the land and freshwater mollusca of Taiwan (Formosa), etc., p. 720. (Description of *Oncomelania formosana*.)

Poirier, G.

1881. Description de quelques espèces nouvelles du cambodge, etc. *Journ. de Conchyl., 29*: 1. (Descriptions of possible species of *Oncomelania;* animal of *Pachydrobia*.)

Prashad, Baini.

1921. The Indian species of the genus *Tricula*, Benson. *Rec. Ind. Mus., 22*: 67.

Quadras, J. F., and von Möllendorff, O. F.

1915. Diagnoses speciorum novarum ex insulis Philippinis. *Nachr. Malak. Gesel. 27*: 105, 138. (Description of Philippine *Triculae*.)

Robson, G. C.

1915. Note on "*Katayama nosophora*." *Brit. Med. Journ.*, (1): 203.

1921. On the anatomy and affinities of *Hypsobia nosophora*. *Ann. Mag. Nat. Hist.* (9), *8*: 401.

Stimpson, W.

1865. Researches upon the Hydrobiinae and allied forms. *Smithsonian Misc. Coll.* No. 201, 29. (The Pomatiopsinae.)

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Addendum.

Since this paper was written and the manuscript sent to America I have received through the courtesy of Dr. Pilsbry paratypes of the following forms described by him:

Pomatiopsis hirasei
Blanfordia simplex
Blanfordia formosana.

In my opinion they fully bear out the synonymy I have given in my paper. *B. simplex* is undoubtedly a synonym of *B. bensoni* Adams as identified by Adams himself and the paratype sent me by Dr. Pilsbry has a varix at least as well developed as it is in Adams's specimen in the Indian Museum. *B. japonica* is, I still think, distinct from any form seen by Pilsbry.

I have also received, still more recently, further Chinese specimens (in spirit) of *Oncomelania nosophora*. They were taken on November 10th at Shaohsing, Chekiang, in very grassy and mossy spots just above the edge of a canal fed by a mountain stream. A pair were observed *in copula*. The fact is important as indicating that the species, at any rate at Shaohsing, is late in hibernating and probably lays its eggs on becoming active in spring. The specimens were sent by Dr. C. H. Barlow, to whom I desire to express my thanks.

Calcutta,
December 19, 1923.

EXPLANATION OF FIGURES. (Plate XXXVI.)

Tricula gregoriana sp. nov.

1. Lateral view of the type specimen from the upper Mekong; × 12.
2. Mouth of the same shell; × *ca.* 16.

Oncomelania formosana (Pilsbry and Hirase).

3. Lateral view of a shell with the apex slightly eroded; × 6.
4. Apex of a young shell (complete); × 15.
5. Mouth of an adult shell; × 13.

Oncomelania nosophora (Robson).

6. Lateral view of a Japanese shell (topotype) in average condition; × 6.
7. Apex of a very nearly complete shell from the same locality; × 15.
8. Mouth of an adult shell; × 13.

Oncomelania hupensis Gredler.

9. Lateral view of a shell from Kiangsu; × 6.
10. Apex of a complete shell from the same locality; × 15.
11. Mouth of an adult shell; × 13.

Blanfordia bensoni (A. Adams).

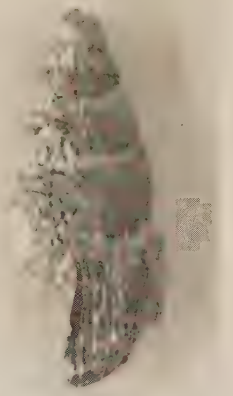
12. Lateral view of a shell (topotype and probably paratype) named by Adams; × 6.
13. Apex of the same shell; × 15.
14. Mouth of the same shell; × 13.

Blanfordia japonica (A. Adams).

15. Lateral view of a shell (topotype and probably paratype) named by A. Adams; × 6.
16. Apex of the same shell; × 15.
17. Mouth of the same shell; × 13.

Melania (Semisulcospira) cancellata (Benson).

18. Lateral view of a shell from Chusan named by Benson (paratype); × *ca.* 2.
19. Mouth of the same shell; × 5.



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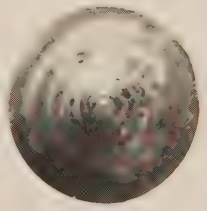

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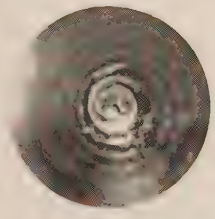

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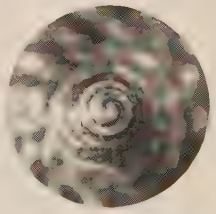

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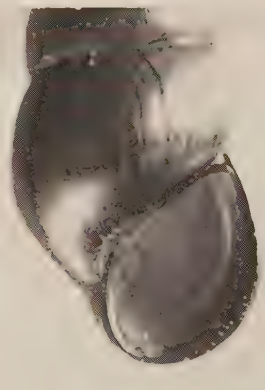

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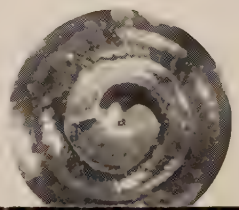

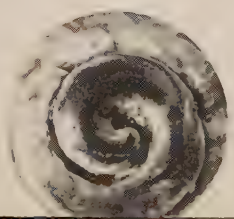

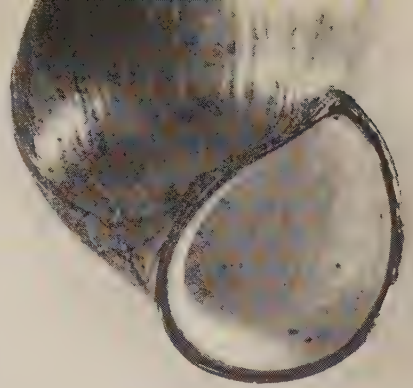

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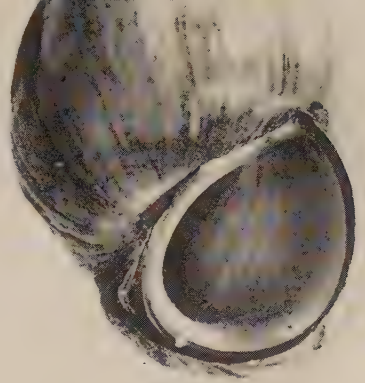

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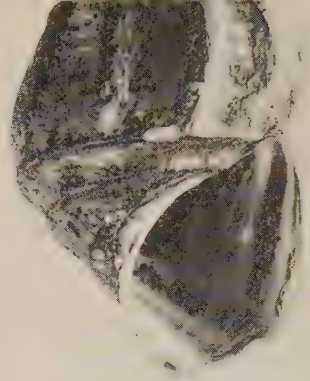

19

(Faust and Meleney: Studies on Schistosomiasis Japonica, Appendix A.)

STUDIES ON SCHISTOSOMIASIS JAPONICA.

APPENDIX B.

The Literature of Schistosomiasis Japonica.

1. Bibliography.

(Historically arranged.)

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1884.

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1886.

Oka, B.

1886. Diagnosis and prophylaxis of endemic diseases. Chū-gai Iji Shimpo (Internat. Med. News), Nos. 161, 162. Japanese text.

1888.

Mashima, E.

1888. A curious case of cirrhosis of the liver, caused by the eggs of a parasite. Tokyo Igakai Zasshi (Jour. Tokyo Med. Assn.), 2, Nos. 16–17. Japanese text.

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Horiuchi, T.

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Yamagiwa, K.

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YAMAGIWA, K.

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1893.

KURIMOTO, T.

1893. Description of the eggs of a new parasite. Tokyo Igakai Zasshi (Jour. Tokyo Med. Assn.), 7 (Nos. 22–23). Japanese text.

1895.

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1895. A case of cirrhosis of the liver from the eggs of Distoma pulmonale. Tokyo Igakai Zasshi (Jour. Tokyo Med. Assn.), 9 (No. 13). Japanese text.

SUZUKI, T.

1895. A case of pathological changes from the eggs of distoma pulmonale. Tokyo Iji Shinshi (Tokyo Med. Weekly), No. 916. Japanese text.

1896.

OZAWA, S.

1896. Endemic ascites. Kyochū I-ho (Kyochū Med. Jour.), No. 60, also in Dai Nippon Shiritsu Eisei Kai Yamanashi Shikai Kaiho (Jour. Yamanashi Branch of Jap. Health Soc.), No. 8. Japanese text.

YAMAGUCHI, H.

1896. Description of the endemic disease of the Katayama region, Yasuna district, Hiroshima Prefecture. Saikingaku Zasshi (Jour. of Bacteriol.), No. 12. Japanese text.

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KANAMORI, T.

1898. Contribution to the aetiology of tumors. Tokyo Igakai Zasshi (Jour. Tokyo Med. Assn.), 12 (No. 2). Japanese text.

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